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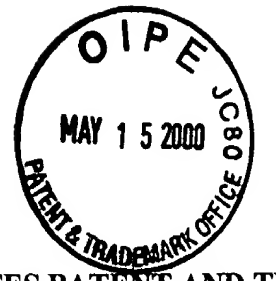

Attorney Docket No.: 5686.200-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Teng et al.

Serial No.: 09/483,504 Group Art Unit: 1614

Filed: January 14, 2000 Examiner: To be assigned

For: Non-Peptide GLP-1 Agonists

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I hereby certify that the attached correspondence comprising:

1. Claim to Convention Priority

is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner of Patents and Trademarks
Washington, DC 20231

on May 9, 2000.

Carol McFarlane
(name of person mailing paper)

Carol McFarlane
(signature of person mailing paper)

Attorney Docket No.: 5686.200-US

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Examiner: To be assigned

For: Non-Peptide GLP-1 Agonists

CLAIM TO CONVENTION PRIORITY UNDER 35 U.S.C. 119

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

In the matter of the above-identified application and under the provision of 35 U.S.C. 119, Applicants claim priority of application Serial No. 09/483,504 filed on January 14, 2000 in Danish application no. PA 1999 00041 filed on January 15, 1999. Applicants submit a duly certified copy of said foreign application.

Respectfully submitted,

Date: May 9, 2000

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Patent application No.: PA 1999 00041

Date of filing: 15 January 1999

Applicant: Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd

This is to certify the correctness of the following information:

The attached photocopy is a true copy of the following information:

- The specification, claims and abstract as filed with the application on the filing date indicated above.

Patent- og Varemærkestyrelsen · Kongeriget Danmark ·

Patent- og

NON-PEPTIDE GLP-1 AGONISTS

FIELD OF THE INVENTION

The present invention relates to novel non-peptide GLP-1 agonists, pharmaceutical compositions comprising them, use of the non-peptide GLP-1 agonists for the preparation of pharmaceutical compositions and methods for the treatment and/or prevention of disorders and diseases wherein an activation of the human GLP-1 receptor is beneficial, especially metabolic disorders such as IGT (impaired glucose tolerance), Type 1 diabetes, Type 2 diabetes and obesity.

BACKGROUND OF THE INVENTION

GLP-1 (glucagon like peptide-1) is a 30 amino acid long peptide hormone secreted by the L-cells in the intestine.

GLP-1 consists of two native forms, GLP-1 (7-36) and GLP-1 (7-37), of the following amino acid sequences:

```
 7   8   9  10  11  12  13  14  15  16  17
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-

18  19  20  21  22  23  24  25  26  27  28
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-

29  30  31  32  33  34  35  36
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X
```

wherein X is NH_2 for GLP-1(7-36) and Gly for GLP-1(7-37).

GLP-1 is a so-called incretin and its primary mechanisms of actions are to:

- Stimulate insulin secretion in a physiological and glucose-dependent manner.
- Decrease glucagon secretion.
- Inhibit gastric emptying.

Stimulating insulin secretion and at the same time decreasing glucagon secretion is probably what makes GLP-1 a very efficient blood glucose lowering agent (1). The very efficient blood glucose lowering as well as the glucose dependency of its action makes it an ideal candidate for the treatment of Type 2 diabetes (2-10). Furthermore, it may be useful for the treatment of Type 1 diabetes in combination with insulin (11). GLP-1 offers something that no other existing drug or drug candidate can provide: very efficient blood glucose lowering, even in SU (sulphonylurea)-failures (6), without the risk of serious hypoglycaemia. Apart from these major effects, GLP-1 has also been shown to increase the rate of insulin biosynthesis (12,13) and restore the ability of the β-cells to respond rapidly to rising plasma glucose in terms of first phase insulin release in rats (14). Thus, GLP-1 would be expected to be able to prevent or delay the progression from IGT to full blown Type 2 diabetes. Patients treated with GLP-1 compared to eg metformin or sulphonylureas, will be better managed and may as a result thereof have a much later transfer to insulin requiring therapy.

The importance of the GLP-1 receptor in regulating insulin secretion was illustrated in recent experiments in which a targeted disruption of the GLP-1 receptor gene was carried out in mice. Animals homozygous for the disruption had greatly deteriorated glucose tolerance and fasting hyperglycaemia, and even heterozygous animals were glucose intolerant (15).

An important and perhaps primary defect in Type 2 diabetes patients may be an impaired incretin function (16,17). In fact, in the rather few patients with Type 2 diabetes so far investigated for this, all had a greatly decreased or absent insulin response to the "other" incretin hormone, namely GIP (Gastric Inhibitory Polypeptide) (17,18). Because GIP is the "first-in-line" incretin and GIP signalling is defective, meal-induced insulin secretion is also defective. This cannot be overcome with endogenous or exogenous GIP because the patients are insensitive to GIP, but it may be compensated for with GLP-1 (18). In contrast to GIP, the insulinotropic action of GLP-1 is preserved in diabetic patients (19). Replacing the incretin deficiency may also be why GLP-1 treatment is so effective.

The ability of GLP-1 to decrease appetite and energy intake is now firmly established, both in normal, lean people and in obese people (20-22). Obese subjects have been shown to have

GLP-1 is described further in WO No 98/20895 to Novo Nordisk A/S and WO No 98/28414 to Eli Lilly and Company.

GLP-1 is rapidly metabolized by the proteolytic enzyme Dipeptidyl Peptidase-IV (25) into an inactive or perhaps even antagonistic metabolite (26), complicating the use of GLP-1 as a drug.

The use of GLP-1 and analogues of GLP-1 as well as fragments thereof in the treatment of Type 1 and Type 2 diabetes and obesity are disclosed in several publications.

Thus, WO No 87/06941 and WO No 90/11296 to The General Hospital Corporation disclose GLP-1 fragments, including GLP-1(7-37) and GLP-1(7-36), and functional derivatives thereof for use as insulinotropic agents.

Furthermore, WO No 91/11457 to Buckley et al. discloses analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37 for use in the treatment of Type 2 diabetes and WO No 98/08871 to Novo Nordisk A/S discloses derivatives of GLP-1 for use in the treatment of diabetes and obesity which are especially useful as they are both metabolically stable and very potent.

However, peptides are generally not known to be orally available.

Best care for patients would obviously be achieved if a drug was orally availabl . The provision of orally available non-peptide GLP-1 agonists would therefore constitute a highly valuable contribution to the art.

The GLP-1 receptor is a so-called 7 transmembrane (7TM) G-protein coupled receptor.

US No 5,670,360 to Novo Nordisk A/S discloses the cloning and use of the GLP-1 receptor. Five superfamilies of these receptors are known. Of these the glucagon-secretin (B) family consists of the receptors for GLP-1, glucagon, GIP, secretin, VIP, PACAP, calcitonin, PTH, CRF, GRF and a few more.

The (B) family is characterised by a relative large N-terminal domain of the receptor. The natural ligands for these receptors are all large peptides and the binding (and consecutive activation) of the receptors by their natural ligands is believed to involve both the N-terminal domain and the transmembrane region.

Small non-peptide agonists for peptide receptors are generally considered very difficult to find.

The above characteristics of the (B) family receptors seem to further complicate the provision of an agonist and so far no small non-peptide agonists have been described for a receptor in the (B) family.

However, surprisingly we have found a whole new class of non-peptide GLP-1 agonists which activate the human GLP-1 receptor.

They may be characterised by activating the human GLP-1 receptor without competing with GLP-1 for the GLP-1 binding site in a competition binding assay.

Furthermore, experiments have shown that the affinity of the receptor for GLP-1 changes upon incubation with some of the compounds according to the invention.

It is believed that the compounds of the invention stabilize another conformation of the receptor than that stabilized by GLP-1.

G-protein coupled receptors are theoretically thought to exist in different conformations: R and R*, where R is the inactive receptor conformation and R* the active. The most recent literature speculates that there may be one or more intermediate states (29).

One understanding of antagonists and inverse agonists is that they are able to bind to and stabilize the inactive conformation of the receptor whereas agonists bind to and stabilize the active conformation. It is not really known what a partial agonist does in these models.

The compounds according to the invention may introduce a new model in order to accommodate their characteristics. In this model we introduce a further receptor conformation R** which is another active receptor conformation.

R* would then be the conformation that GLP-1 under normal circumstances stabilizes where R** is the conformation that the compounds according to the invention stabilizes. A model with two different active receptor conformations may also offer an explanation for why some of the compounds according to the invention when tested in the assays are partial and not full agonists because one conformation may be able to elicit partial agonism only and the other full agonism.

DEFINITIONS

The following is a detailed definition of the terms used to describe the compounds of the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

The term "lower alkyl" in the present context designates a saturated, branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "lower alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, isopropenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-

The term "lower alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "cycloalkyl" as used herein represents a carbocyclic group having from 3 to 10 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

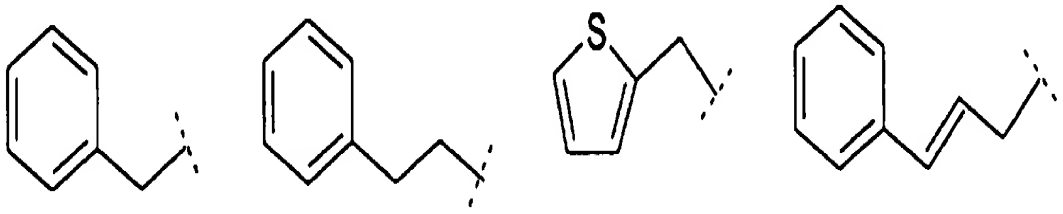
The term "cycloalkenyl" as used herein represents a carbocyclic group having from 3 to 10 carbon atoms containing at least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

The term "heterocyclyl" as used herein represents a saturated or partially unsaturated 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "aryl" as used herein represents a carbocyclic aromatic ring system such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl,

oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

"Aryl-lower alkyl", "heteroaryl-lower alkyl", "aryl-lower alkenyl" etc. mean a lower alkyl or alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:



The above cycloalkyl, cycloalkenyl, heterocyclyl, aryl and heteroaryl ring systems may optionally be substituted by one or more substituents, for example selected from the group consisting of halogen; lower alkyl; lower alkanoyl such as formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the like; -OH;- CH_2OH; $-NO_2$; -CN; $-CO_2H$; -O-lower alkyl; aryl-lower alkyl;

acids including derivatives thereof wherein one or more of the amino acid residues have been chemically modified, eg by alkylation, acylation, ester formation or amide formation.

Within the context of the present invention, a GLP-1 agonist is understood to refer to any compound which fully or partially activates the human GLP-1 receptor.

Within the context of the present invention, a partial GLP-1 agonist is understood to refer to any compound which increases the activity of the human GLP-1 receptor but which compared to GLP-1 is not able to effect a full response (E_{max} < 100% relative to GLP-1).

Within the context of the present invention, a GLP-1 antagonist is understood to refer to any compound which decreases the activity of the human GLP-1 receptor seen after stimulation with GLP-1.

Within the context of the present invention an inverse GLP-1 agonist is understood to refer to any compound which not only decreases the activity of the human GLP-1 receptor seen after stimulation with GLP-1 but also decreases the activity of the non-stimulated receptor (basal activity).

Within the context of the present invention a metabolic disorder is understood to refer to any disorder associated with the metabolism or resulting from a defect of the metabolism.

Within the context of the present invention GLP-1 is understood to refer to either or both of the above two native forms GLP-1 (7-36) and GLP-1 (7-37) unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a compound of the general formula (I):

wherein

R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^5$, lower alkyl, $-SR^5$, $-S(O)_2NR^5R^6$, $-S(O)NR^5R^6$, $-S(O)_2R^5$, $-C(O)NR^5R^6$, $-CH_2OR^5$, $-CH_2NR^5R^6$ or $-C(O)OR^5$;

wherein R^5 and R^6 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^5 and R^6 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

one of X and V is =N-; and the other is =CD- or =N-;

wherein D is hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^7$, $-NR^7R^8$, lower alkyl, aryl, $-C(O)NR^7R^8$, $-CH_2OR^7$, $-CH_2NR^7R^8$ or $-C(O)OR^7$;

wherein R^7 and R^8 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^7 and R^8 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

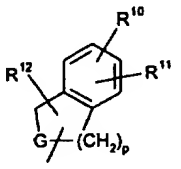
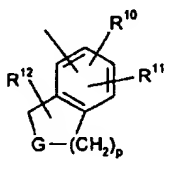
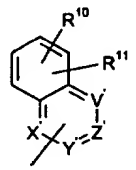
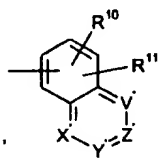
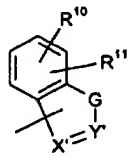
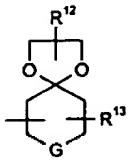
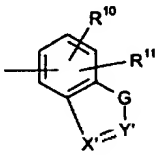
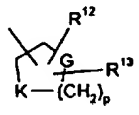
L and M independently are a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mO(CH_2)_n-$,

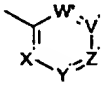
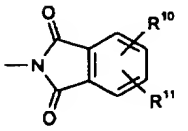
$-(CH_2)_mC(NOR^9)(CH_2)_n-$, $-(CH_2)_mNR^9S(O)_2(CH_2)_n-$, $-(CH_2)_mS(O)_2NR^9(CH_2)_n-$, $-(CH_2)_mCHOR^9(CH_2)_n-$ or $-(CH_2)_mP(O)(OR^9)O(CH_2)_n-$;

wherein R^9 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl;

m and n independently are 0, 1, 2 or 3;

A and B independently are hydrogen, halogen, $-CF_3$, $-CF_2CF_3$, -CN, $-NO_2$, lower alkyl, lower alkenyl, lower alkynyl,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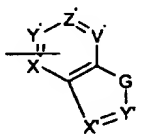


wherein

p is 1, 2 or 3;

X' is -N= or $-CR^{14}$=;

Y' is -N= or -CR^{15}=;

Z' is -N= or -CR^{16}=;

V' is -N= or -CR^{17}=;

W' is -N= or -CR^{18}=;

G is -NR^{19}-, -O- or -S-;

K is -NR^{20} -O- or -S-;

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} independently are hydrogen, halogen, -CN, -CF_3, -OCF_3, -OCH_2CF_3, -OCF_2CHF_2, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, -SCF_3, -SR^{21}, -CHF_2, -$OCHF_2$, -$OS(O)_2CF_3$, -$OS(O)_2R^{21}$, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)_2R^{21}$, -$S(O)R^{21}$, -$(O)NR^{21}R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$ or -$(O)OR^{21}$, where R^{12} and R^{13} furthermore independently may represent oxo; or two of the groups R^{10} to R^{18} when defined in the same ring together may form a bridge -OCH_2O-;

wherein R^{21} and R^{22} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cy-

$R^{19}$and R^{20} independently are hydrogen, -OR^{23}, -$NR^{23}R^{24}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, -C(O)$NR^{23}R^{24}$ or -C(O)OR^{23};

wherein R^{23} and R^{24} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^{23} and R^{24} together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

with the provisos that

when L represents a group wherein n is 0, A is not halogen, -CN or -NO_2; and

when M represents a group wherein n is 0, B is not halogen, -CN or -NO_2;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of

wherein R^1, R^2, R^3, R^4, L, M, A and B are as defined for formula (I).

Preferably, R^1, R^2, R^3 and R^4 are independently hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, lower alkyl, lower alkoxy, $-S(O)_2NR^5R^6$, $-S(O)NR^5R^6$, $-S(O)_2R^5$, $-C(O)NR^5R^6$ or $-C(O)OR^5$, wherein R^5 and R^6 are as defined for formula (I).

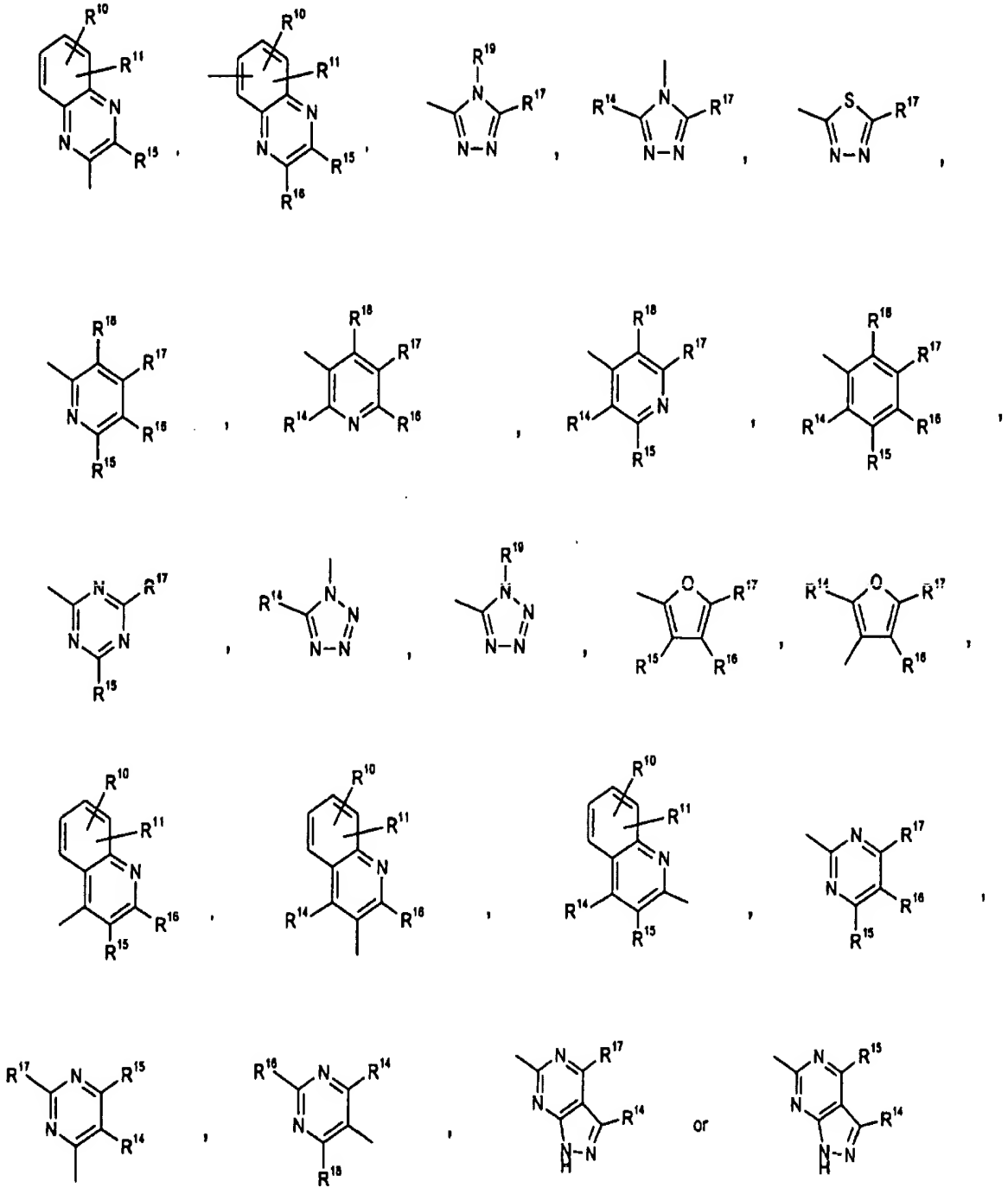
In one preferred embodiment, R^1, R^2, R^3 and R^4 are independently hydrogen, halogen, -CN, $-CF_3$ or $-S(O)_2R^5$, wherein R^5 is as defined for formula (I).

In another preferred embodiment, R^1, R^2, R^3 and R^4 are independently hydrogen, halogen, -CN, $-CF_3$, lower alkyl, lower alkoxy or $-C(O)NR^5R^6$, wherein R^5 and R^6 independently are hydrogen or lower alkyl.

Among these, R^1, R^2, R^3 and R^4 are preferably independently hydrogen, halogen, -CN, lower alkyl or lower alkoxy.

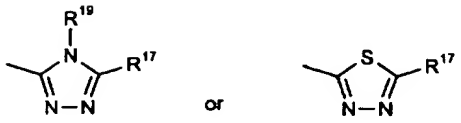
In a further preferred embodiment two of th groups R^1 to R^4 are hydrogen and the other two are different from hydrogen.

Preferably, R^1 and R^4 are both hydrogen and R^2 and R^3 are as defined for formula (I) or as



wherein R^{10}, R^{11}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are as defined for formula (I).

R^{10}, R^{11}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are preferably independently selected from hydrogen, halogen, lower alkyl, $-NH_2$, $-CF_3$,-CN, -S-(cycloalkyl-lower alkyl),-NHC(O)(cycloalkyl-lower alkyl), $-C(O)NH_2$, -S-lower alkyl, -O-lower alkyl, phenyl, furanyl, thienyl, -NHC(O)O-lower al-



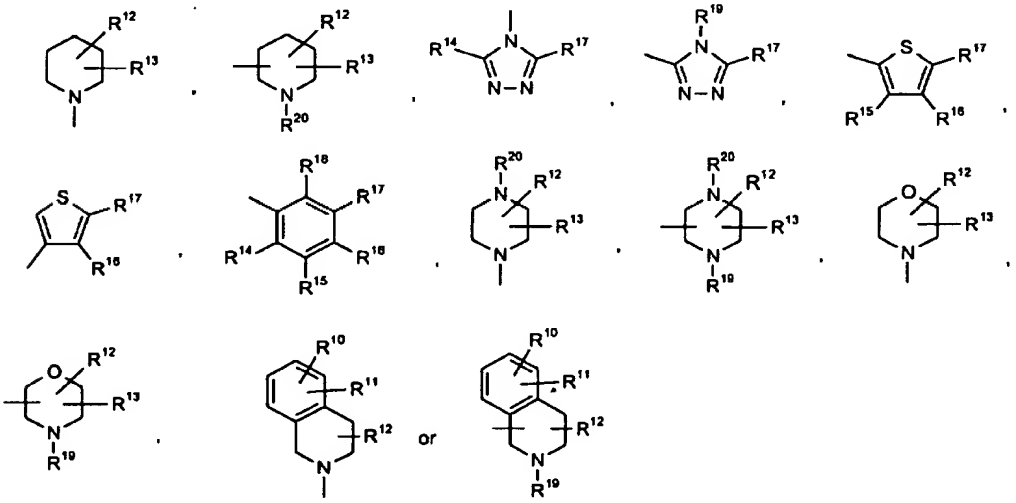
wherein R^{17} and R^{19} are as defined for formula (I) or in the above preferred embodiments thereof. R^{17} is preferably lower alkyl, $-NH_2$ or -S-lower alkyl and R^{19} is preferably hydrogen.

In still a preferred embodiment of the invention M is a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mCH=CH(CH_2)_n-$ or $-(CH_2)_mCHR^9(CH_2)_n-$ wherein m, n and R^9 are as defined for formula (I).

Of these M is preferably a valence bond, $-CH_2S-$, -CH=CH-, $-CH_2CH_2-$ or $-CH_2-$.

Even more preferred M is a valence bond.

In yet another preferred embodiment of the invention B is hydrogen, halogen, $-CF_3$, $-CF_2CF_3$, lower alkyl,



wherein R^{10} to R^{20} are as defined for formula (I).

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are preferably independently selected from hydrogen, halogen, lower alkyl, $-NH_2$, $-CF_3$,-CN, -S-(cycloalkyl-lower alkyl),

-NHC(O)(cycloalkyl-lower alkyl), -C(O)NH_2, -S-lower alkyl, -O-lower alkyl, phenyl, furanyl, thienyl, -NHC(O)O-lower alkyl and -C(O)CH_3. R^{19} and R^{20} are preferably independently selected from lower alkyl and hydrogen.

More preferred B is -CF_3 or lower alkyl.

In a further aspect the invention relates to a compound of the formula (II) as defined above wherein R^2 and R^3 are both either halogen, -CN or -CF_3, L is -$S(CH_2)_n$-, -$S(O)(CH_2)_n$- or -$S(O)_2(CH_2)_n$- wherein n is 0, 1, 2 or 3, and R^1, R^4, A, M and B are as defined for formula (I) or as defined in the above preferred embodiments thereof.

In another aspect the invention relates to a compound of the formula (II) as defined above wherein L is -$S(CH_2)_n$-, -$S(O)(CH_2)_n$- or -$S(O)_2(CH_2)_n$-, wherein n is 0, 1, 2 or 3, M is a valence bond, B is -CF_3 or isopropyl, and R^1, R^2, R^3, R^4 and A are as defined for formula (III) or as defined in the above preferred embodiments thereof, with the proviso that when R^1, R^2, R^3 and R^4 are hydrogen, B is isopropyl and L is -SCH_2-, A must not be hydrogen.

In still another aspect the invention relates to a compound of the formula (II) as defined above wherein L is -$S(CH_2)_n$-, -$S(O)(CH_2)_n$- or -$S(O)_2(CH_2)_n$-, wherein n is 0, 1, 2 or 3, at least one of the groups R^2 and R^3 are -CN, and R^1, R^4, A, M and B are as defined for formula (I) or as defined in the above preferred embodiments thereof.

In still another aspect the invention relates to a compound of the formula (II) as defined above wherein L is -$S(CH_2)_n$-, -$S(O)(CH_2)_n$- or -$S(O)_2(CH_2)_n$-, wherein n is 0, 1, 2 or 3, R^1, R^2, R^3 and R^4 are as defined for formula (I), A is a heterocyclic ring, and

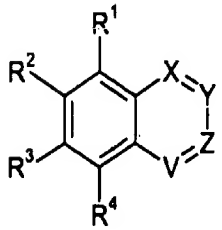
M is -CH_2S-, -CH=CH-, -CH_2CH_2- or -CH_2-, and B is as defined for formula (I) above or as defined in the above preferred embodiments thereof, or

M is a valence bond, and B is -CF_3, -CN, lower alkyl, lower alkenyl, lower alkynyl or halogen.

The compounds according to the invention are preferably characterised by having a molecular weight of up to 1000, preferably of up to 600.

Preferably, the compounds according to the invention have an EC_{50} value as determined by the method for determining the ability to stimulate cAMP formation in a cell line expressing the cloned human GLP-1 receptor disclosed in the following of less than 25 μM, such as of less than 10 μM, more preferred of less than 2 μM and even more preferred of less than 1 μM.

In a further aspect the invention relates to to a compound of an EC_{50} value as determined by the method for determining the ability to stimulate cAMP formation in a cell line expressing the cloned human GLP-1 receptor disclosed herein of less than 25 μM and having the general formula (III):



(III)

wherein

R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^5$, $-NR^5R^6$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocyclyl, heteroaryl, $-SR^5$, $-NR^5S(O)_2R^6$, $-S(O)_2NR^5R^6$, $-S(O)NR^5R^6$, $-S(O)_2R^5$, $-C(O)NR^5R^6$, $-CH_2OR^5$, $-CH_2NR^5R^6$ or $-C(O)OR^5$;

wherein R^5 and R^6 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^5 and R^6 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

X, Y, Z and V independently are =N-; =C(L-A)-; =C(M-B)- or =CD-; with the proviso that one of X, Y, Z and V is =N-; one is =C(L-A)-; one is =C(M-B)-; and the remaining is =CD- or =N-;

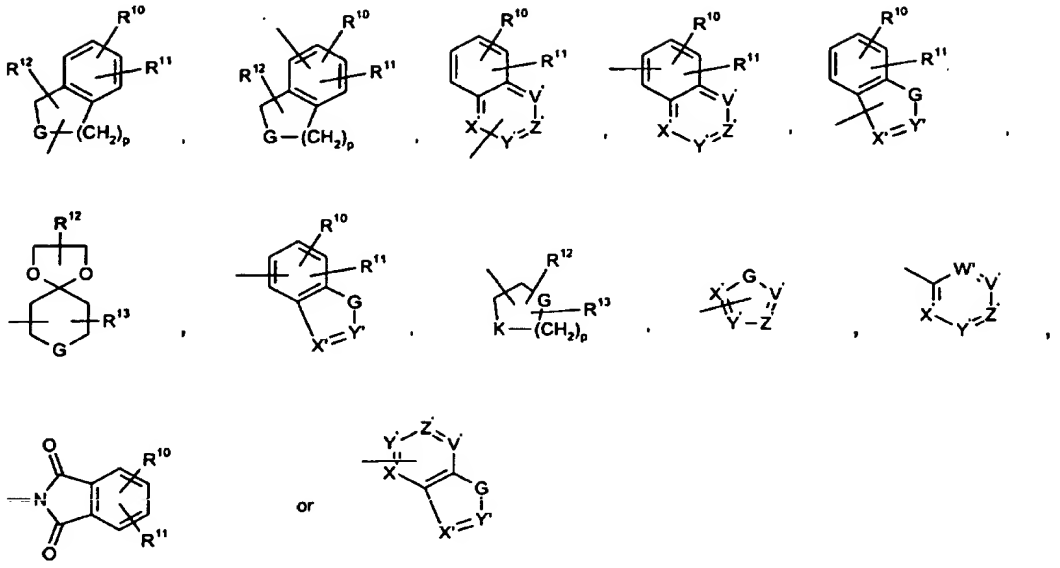
wherein D is hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^7$, $-NR^7R^8$, lower alkyl, aryl, $-C(O)NR^7R^8$, $-CH_2OR^7$, $-CH_2NR^7R^8$ or $-C(O)OR^7$;

wherein R^7 and R^8 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^7 and R^8 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

L and M independently are a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mO(CH_2)_n-$, $-(CH_2)_mS(O)(CH_2)_n-$, $-(CH_2)_mS(O)_2(CH_2)_n-$, $-(CH_2)_mCH=CH(CH_2)_n-$, $-(CH_2)_mC\equiv C(CH_2)_n-$, $-(CH_2)_mCHR^9(CH_2)_n-$, $-(CH_2)_mNR^9(CH_2)_n-$, $-(CH_2)_mC(O)NR^9(CH_2)_n-$, $-(CH_2)_mC(O)O(CH_2)_n-$, $-S(CH_2)_mC(O)O(CH_2)_n-$, $-S(CH_2)_mC(O)NR^9(CH_2)_n-$, $-(CH_2)_mOC(O)(CH_2)_n-$, $-(CH_2)_mC(O)(CH_2)_n-$, $-(CH_2)_mC(NOR^9)(CH_2)_n-$, $-(CH_2)_mNR^9S(O)_2(CH_2)_n-$, $-(CH_2)_mS(O)_2NR^9(CH_2)_n-$, $-(CH_2)_mCHOR^9(CH_2)_n-$ or $-(CH_2)_mP(O)(OR^9)O(CH_2)_n-$;

wherein R^9 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, h terocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl;

m and n independently are 0, 1, 2 or 3;



wherein

p is 1, 2 or 3;

X' is -N= or -CR^{14}=;

Y' is -N= or -CR^{15}=;

Z' is -N= or -CR^{16}=;

V' is -N= or -CR^{17}=;

W' is -N= or -CR^{18}=;

G is -NR^{19}-, -O- or -S-;

K is -NR^{20} -O- or -S-;

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} independently are hydrogen, halogen, -CN, -CF_3, -OCF_3, -OCH_2CF_3, -OCF_2CHF_2, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-

lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, $-SCF_3$, $-SR^{21}$, $-CHF_2$, $-OCHF_2$, $-OS(O)_2CF_3$, $-OS(O)_2R^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)_2R^{21}$, $-S(O)R^{21}$, $-(O)NR^{21}R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$ or $-(O)OR^{21}$, where R^{12} and R^{13} furthermore independently may represent oxo; or two of the groups R^{10} to R^{18} when defined in the same ring together may form a bridge $-OCH_2O-$;

wherein R^{21} and R^{22} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^{21} and R^{22} together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

$R^{19}$and R^{20} independently are hydrogen, $-OR^{23}$, $-NR^{23}R^{24}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, $-C(O)NR^{23}R^{24}$ or $-C(O)OR^{23}$;

wherein R^{23} and R^{24} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^{23} and R^{24} together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing

one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

with the provisos that

when L represents a group wherein n is 0, A is not halogen, $-CF_3$, -CN or $-NO_2$; and

when M represents a group wherein n is 0, B is not halogen, $-CF_3$, -CN or $-NO_2$;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a further aspect the invention relates to a non-peptide GLP-1 agonist which activates the human GLP-1 receptor. Agonist activity may eg be determined by the assay described in Example No 61.

Compounds may also be shown to be active by measuring insulin release from isolated human islets. This can be done according to the method disclosed in Eizirik DL, Korbutt GS, Hellerström C. Prolonged exposure of human pancreatic islets to high glucose concentrations in vitro impairs the beta-cell function. J. Clin. Invest. 90:1263-1268, 1992.

In a preferred embodiment the non-p ptide GLP-1 agonist activates the human GLP-1 re-

GLP-1 in a competition binding assay will not displace the tracer. Therefore, the tracer will display an unchanged binding of 100 % in this assay whereas different concentrations of GLP-1 will compete with the tracer resulting in a decreased binding of the tracer in the range of between 0 and up to 100%.

In a further preferred embodiment the non-peptide GLP-1 agonist potentiates the binding of GLP-1 to the human GLP-1 receptor in a competition binding assay.

Such a potentiating effect may be demonstrated eg by the competition binding assay described above. Compounds that potentiate the binding will result in more than 100% tracer bound.

In a preferred embodiment the non-peptide GLP-1 agonist stabilises an active conformation of the human GLP-1 receptor different from the one(s) which GLP-1 stabilizes.

This may be determined eg by performing a saturation experiment determining the affinity of GLP-1 with and without the presence of the compound in question. The saturation experiment is a standard receptor pharmacology experiment whereby the true affinity of a compound for a receptor can be measured (30). The protocol for the binding assay described above may be used except for that here the tracer is diluted and two sets of samples are measured, one with 10^{-6} M GLP-1 added (to determine non-specific binding) and one without (to determine total binding). The specific binding (total minus non-specific) is then plotted vs the concentration of tracer added. A curve fitting program (eg the saturation/scatchard template in GraphPad Prism®) may then determine the number of binding sites and the affinity. There may be more than one binding site with different affinities. When such an experiment is performed with GLP-1 one may observe one or two different binding sites dependent on the temperature at which the experiment is performed. It may be shown that the compounds in question stabilize a conformation different from that which GLP-1 normally stabilizes by p rforming the saturation xperiment described above in the presence of a high concentration of the compound in question. If the affinity of GLP-1 for the receptor is different when the compound is present, then the compound must stabilize a conformation of the receptor different from the one(s)

The non-peptide GLP-1 agonists according to the invention may be either partial or full agonists.

In a further preferred embodiment the non-peptide GLP-1 agonist is a partial agonist.

Such partial agonists may be less likely of causing the receptor to desensitize because they do not fully activate the receptor and therefore also do not fully activate the desensitization signals.

Preferably, the non-peptide partial agonists have an E_{max} of less than 90%, preferably less than 80% and more preferred in the range of 35 to 75% of that of GLP-1.

This may be determined eg by the assay described in Example No 61.

However, agonists of an E_{max} of 90% or more as well as full agonists being efficient at lower dosages may also be usable. Thus, in another preferred embodiment the non-peptide GLP-1 agonist is a full agonist.

The non-peptide GLP-1 agonists have the advantage of being selective towards the human GLP-1 receptor. Accordingly, in still a further preferred embodiment the non-peptide GLP-1 agonist has at least a 10 fold selectivity towards the human GLP-1 receptor compared to the human glucagon receptor and/or the human GIP receptor. This may be determined eg by the assay described in Example No 61 using cells expressing the human glucagon receptor and/or the human GIP receptor and comparing the formation of cAMP with the amount obtained using the cells expressing the human GLP-1 receptor.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included in the scope of the invention.

Furthermore, when a double bond is present in the molecule geometric isomers may be

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms which the compounds are able to form are included in the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

The compounds according to the present invention activate the human GLP-1 receptor and are accordingly useful for the treatment and/or prevention of disorders and diseases in which such an activation is beneficial.

Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment and/or prevention of a disorder or disease wherein an activation of the human GLP-1 receptor is beneficial.

The invention also relates to a method for the treatment and/or prevention of disorders or diseases wherein an activation of the human GLP-1 receptor is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

Owing to the efficiency of the present compounds to activate the human GLP-1 receptor they are useful for the treatment and/or prevention of disorders and diseases, such as metabolic disorders, wherein an activation of the said receptor is beneficial. Accordingly, they may find use in the treatment and/or prevention of hyperglycaemia, dyslipidemia, Type 1 diabetes, Type 2 diabetes, hypertriglyceridemia, syndrome X, insulin resistance, impaired glucose tolerance, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, hyperlipidemia,

psychosis, seizures, panic attacks, hysteria or sleep disorders. A further application is for the inhibition of intestinal motility.

In a preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

In a further preferred embodiment of the invention the present compounds are used for the

such as those disclosed in WO 98/08871 to Novo Nordisk A/S which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers, insulin sensitizers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid metabolism, compounds lowering food intake, PPAR and RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells.

In a preferred embodiment of the invention the present compounds are administered in combination with insulin.

In a further preferred embodiment the present compounds are administered in combination with a sulphonylurea selected from tolbutamide, glibenclamide, glipizide and glicazide.

In another preferred embodiment the present compounds are administered in combination with metformin.

In still another preferred embodiment the present compounds are administered in combination with a thiazolidinedione selected from troglitazone, ciglitazone, pioglitazone, rosiglitazone and the compounds disclosed in WO No 97/41097 to Dr. Reddy's Research Foundation, especially 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]-methyl]-2,4-thiazolidinedione.

In a further preferred embodiment the present compounds are administered in combination with acarbose.

In yet a preferred embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells selected from glibenclamide, glipizide, glicazide and repaglinide.

Furthermore, the compounds according to the invention may be administered in combination

Such agents may be selected from the group consisting of CART agonists, NPY antagonists, MC4 agonists, orexin antagonists, H3 antagonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH agonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, glucagon, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR β agonists.

In a preferred embodiment of the invention the antiobesity agent is leptin.

In another preferred embodiment the antiobesity agent is amphetamine.

In another preferred embodiment the antiobesity agent is dexfenfluramine.

In still another preferred embodiment the antiobesity agent is sibutramine.

In a further preferred embodiment the antiobesity agent is orlistat.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses.
The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy,19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any

and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the na-

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosag forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by meth-

ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	5.0 mg
Lactosum Ph. Eur.	67.8 mg
Cellulose, microcryst. (Avicel)	31.4 mg
Amberlite	1.0 mg
Magnesii stearas Ph. Eur.	q.s.
Coating:	
HPMC approx.	9 mg
Mywacett 9-40 T* approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula (I) in combination with further pharmacologically active substances such as those described in the foregoing.

The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

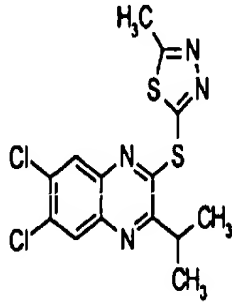
EXAMPLES

Abbreviations:

APCI: Atm. Pressure Chemical Ionisation

EXAMPLE 1

6,7-Dichloro-2-isopropyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline



To a solution of 2,6,7-trichloro-3-isopropylquinoxaline (51 mg, 0.18 mmol) in dimethylformamide (4 ml) was added potassium fluoride/alumina (80 mg, 0.55 mmol) followed by 2-mercapto-5 methyl-1,3,4-thiadiazole (26 mg, 0.20 mmol). The reaction was stirred at room temperature overnight. The reaction was stirred at room temperature overnight. The product was purified by flash column chromatography using ethyl acetate:hexanes 1:5 affording the title compound as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.42 (d, 6H), 2.89 (s, 3H), 3.42 (m, 1H), 8.06 (s, 1H), 8.17 (s, 1H).

MS (APCI $(M+H)^+$) m/z 371.

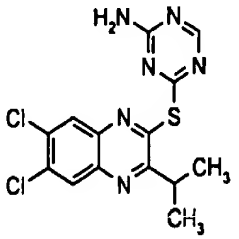
EXAMPLE 2

^{1}H NMR ($CDCl_3$): δ 2.92 (s, 3H), 8.12 (s, 1H), 8.31 (s, 1H).

MS (APCI $(M+H)^+$) m/z 397.

EXAMPLE 3

6,7-Dichloro-2-isopropyl-3-(4-amino-1,3,5-triazin-2-ylsulfanyl)quinoxaline



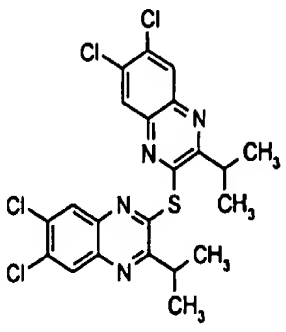
Using the same procedure as described above the title compound was obtained as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.18 (d, 6H), 3.50 (m, 1H), 8.33 (s, 1H), 8.37 s, 1H).

MS (APCI $(M+H)^+$) m/z 367.

EXAMPLE 4

bis-(6,7-Dichloro-2-isopropylquinoxalin-3-yl)sulfide



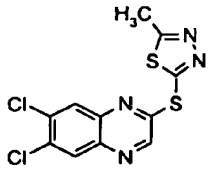
To a solution of 2,6,7-trichloro-3-isopropylquinoxaline (105 mg, 0.38 mmol) in dimethylformamide (3 ml) was added sodium hydrosulfide (21 mg, 0.23 mmol). The reaction was stirred

matography using ethyl acetate:hexanes 1:60. Extraction of the product band using chloroform afforded th title compound as a white solid in 20% yield.

^{1}H NMR ($CDCl_3$): δ 1.40 (d, 6H), 3.53 (m, 1H), 7.86 (s, 1H),. 8.20 (s, 1H).
MS (APCI $(M+H)^+$) m/z 511.

EXAMPLE 5

6,7-Dichloro-2-(5-methyl-1,3,4-thiadiazol-2-yl-sulfanyl)quinoxaline

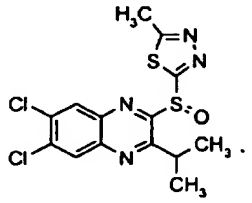


To a solution of 2,6,7-trichloroquinoxaline (60 mg, 0.26 mmol) in DMF (4 ml) was added 40% wt potassium fluoride over alumina (112 mg, 0.77 mmol), causing the burgundy solution to turn amber. 2-Mercapto-5-methyl-1,3,4-thiadizole (34 mg, 0.26 mmol) was then added and the solution became reddish amber. The reaction was capped and stirred at room temperature, overnight. The product was purified by flash column chromatography using ethyl acetate:hexanes (1:3) to afford the title compound.

^{1}H NMR ($CDCl_3$): δ 2.89 (s, 3H), 8.13 (s, 1H), 8.22 (s, 1H), 8.78 (s, 1H).
MS (APCI $(M+H)^+$) m/z 328.9.

EXAMPLE 6

6,7-Dichloro-2-isopropyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfinyl)quinoxaline



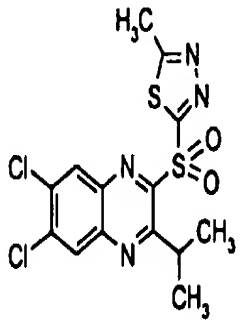
To a solution of the above example 1 6,7-dichloro-2-isopropyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline (168 mg, 0.45 mmol) in dichloromethane (6 ml) was added 3-chloroperoxybenzoic acid (142 mg, 0.45 mmol) while stirring in a dry ice/acetone bath (-78° C). After 8.5 hours, the reaction was quenched by addition of a saturated solution of sodium bicarbonate. The layers were separated and the aqueous layer was extracted twice with chloroform. Removal of the solvent by evaporation yielded a light yellow solid. The product was purified by flash column chromatography using ethyl acetate:hexanes 1:3 to afford the title compound.

^{1}H NMR ($CDCl_3$): δ 1.38 (d, 3H), 1.45 (d, 3H), 2.82 (s, 3H), 3.84 (m, 1H), 8.26 (s, 1H), 8.36 (s, 1H).

MS (APCI $(M+H)^+$) m/z 386.9.

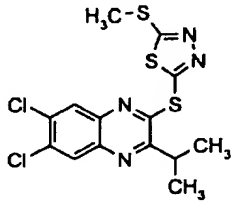
EXAMPLE 7

6,7-Dichloro-2-isopropyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfonyl)quinoxaline



To a solution of 6,7-dichloro-2-isopropyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline

6,7-Dichloro-2-isopropyl-3-(5-methylsulfanyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline

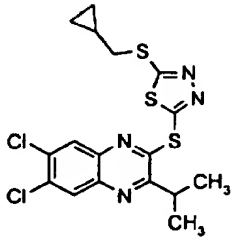


To a solution of 2,6,7-trichloro-3-isopropylquinoxaline (69 mg, 0.25 mmol) in dimethylformamide (4 ml) was added potassium fluoride/alumina (109 mg, 0.75 mmol) followed by addition of 2-mercapto-5-methylsulfanyl-1,3,4-thiadiazole (44 mg, 0.26 mmol). The reaction was stirred overnight at room temperature. The product was purified by flash column chromatography using ethyl acetate:hexanes 1:20 to afford the title compound.

^{1}H NMR ($CDCl_3$): δ 1.43 (d, 6H), 2.87 (s, 3H), 3.41 (m, 1H), 8.09 (s, 1H), 8.18 (s, 1H).
MS (APCI $(M+H)^+$) m/z 403.4.

EXAMPLE 9

6,7-Dichloro-2-isopropyl-3-(5-cyclopropylmethylsulfanyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline



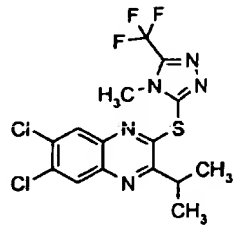
To a solution of 2,6,7-trichloro-3-isopropylquinoxaline (65 mg, 0.23 mmol) in dimethylformamide (4 ml) was added potassium fluoride/alumina (103 mg, 0.71 mmol) followed by addition of (2-cyclopropylmethylsulfanyl-5-mercapto-1,3,4-thiadiazole (53 mg, 0.26 mmol). The reaction was stirred overnight at room temperature. The product was purified by flash column chromatography using ethyl acetate:hexanes 1:20 affording the title compound.

^{1}H NMR ($CDCl_3$): δ 0.39 (m, 2H), 0.68 (m, 2H), 1.31 (m, 1H), 1.43 (d, 6H), 3.37 (m, 3H), 8.10 (s, 1H), 8.18 (s, 1H).

MS (APCI $(M+H)^+$) m/z 442.9.

EXAMPLE 10

6,7-Dichloro-2-isopropyl-3-(4-methyl-5-trifluoromethyl-4H-1,2,4-triazol-3-ylsulfanyl)quinoxaline



To a solution of 2,6,7-trichloro-3-isopropylquinoxaline (64 mg, 0.23 mmol) in dimethylformamide (4 ml) was added potassium fluoride/alumina (1.1 mg, 0.70 mmol) followed by addition of 3-mercapto-5-trifluoromethyl-1,2,4-triazole (43 mg, 0.24 mmol). The reaction was stirred overnight at room temperature. Purification by flash column chromatography using ethyl acetate:hexanes 1:5 (83% yield) afforded 6,7-dichloro-2-isopropyl-3-(5-trifluoromethyl-4H-1,2,4-triazol-3-ylsulfanyl)quinoxaline.

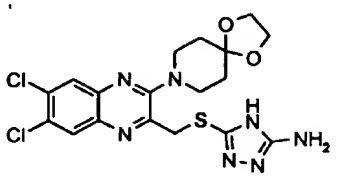
To a solution of the above 6,7-dichloro-2-isopropyl-3-(5-trifluoromethyl-4H-1,2,4-triazol-3-ylsulfanyl)quinoxaline (78 mg, 0.19 mmol) in tetrahydrofuran (5 ml) was added triethylamine (0.05 ml, 0.38 mmol) followed by addition of iodomethane (0.02 ml, 0.29 mmol). The reaction was stirred under nitrogen, overnight, at room temperature. Purification by flash column chromatography using ethyl acetate:hexanes 1:10 afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 1.45 (d, 6H), 3.37 (m, 1H), 4.03 (s, 3H), 7.78 (s, 1H), 8.15 (s, 1H).

MS (APCI $(M+H)^+$) m/z 422.

EXAMPLE 11

5-[6,7-Dichloro-3-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)quinoxalin-2-ylmethylsulfanyl]-4H-1,2,4-triazol-3-ylamine

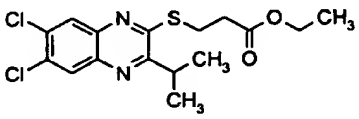


To a solution of 2,6,7-trichloro-3-chloromethylquinoxaline (107 mg, 0.38 mmol) in dimethylformamide (5 ml) was added 3-amino-5-mercapto-1,2,4-triazole (44 mg, 0.38 mmol) followed by addition of triethylamine (0.05 ml, 0.38 mmol). After 5 hours, potassium fluoride/alumina (143 mg, 1.1 mmol) was added, followed by 1,4 dioxa-8-aza-spiro[4.5]decane (0.05 ml, 0.42 mmol). The reaction was stirred overnight at room temperature. Purification by flash column chromatography using ethyl acetate afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 1.87 (m, 4H), 3.48 (m, 4H), 3.99 (s, 4H), 4.56 (s, 2H), 7.92 (s, 1H), 7.99 (s, 1H).
MS (APCI $(M+H)^+$) m/z 468.1.

EXAMPLE 12

3-(6,7-Dichloro-3-isopropylquinoxalin-2-ylsulfanyl)-propionic acid ethyl ester



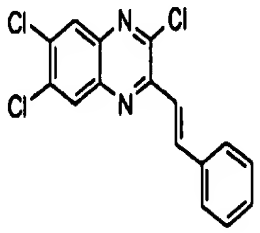
To a solution of 6,7-dichloro-3-isopropylquinoxaline-2-thiol (36 mg, 0.13 mmol) in dimethylformamide was added potassium carbonate (55 mg, 0.40 mmol) followed by ethyl 3-bromopropionate (0.02 ml, 0.16 mmol). The reaction was stirred at room temperature for 4 days. Purification by flash column chromatography using ethyl acetate:hexanes 1:40 afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H), 1.34 (d, 6H), 2.82 (m, 2H), 3.37 (m, 1H), 3.52 (m, 2H), 4.20 (m, 2H), 8.00 (s, 1H), 8.09 (s, 1H).
MS (APCI $(M+H)^+$) m/z 373.

The following examples No 13 to 17 are also useful as intermediates for the preparation of further compounds according to the invention.

EXAMPLE 13

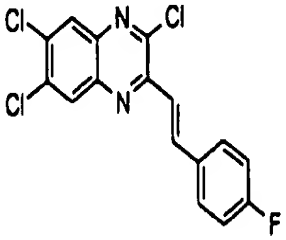
2,6,7-Trichloro-3-styrylquinoxaline



This compound was prepared according to the procedure described in: Collins, J. L.; Dambek, P. J.; Goldstein, S. W.; Faraci, W. S. *Bioorg. Med. Chem. Lett.* **1992**, 2, 915-8.

EXAMPLE 14

2,6,7-Trichloro-3-[2-(4-fluorophenyl)vinyl]quinoxaline



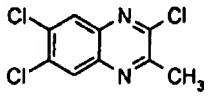
6,7-Dichloro-3-methyl-1H-quinoxalin-2-one (5 g, 22 mmol) (prepared as described in: Collins,

The above 6,7-dichloro-3-[2-(4-fluorophenyl)vinyl]-1H-quinoxalin-2-one (2.0 g, 6 mmol), 4-dimethylaminopyridine (0.2 g) and phosphorous oxychloride ($POCl_3$) was mixed and refluxed for 30 minutes. After cooling, the mixture was poured onto ice (500 ml). The solid was filtered, washed with water and dried *in vacuo* at 30°C over night to afford 1.8 g (83%) of 2,6,7-trichloro-3-[2-(4-fluorophenyl)vinyl]quinoxaline.

^{1}H NMR (DMSO-d_6): δ 7.34 (t, 2H), 7.71 (d, 1H), 7.92 (dd, 2H), 8.05 (d, 1H), 8.40 (s, 1H), 8.45 (s, 1H).

EXAMPLE 15

2,6,7-Trichloro-3-methylquinoxaline

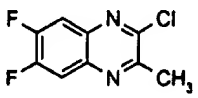


6,7-Dichloro-3-methyl-1H-quinoxalin-2-one (10 g, 44 mmol) and 4-dimethylaminopyridine (1 g) was added $POCl_3$ and the mixture was refluxed ½ hour. After cooling, the mixture was poured onto ice (500 ml), filtered and washed with water to afford the title compound.

^{1}H NMR (DMSO-d_6): δ 2.79 (s, 3H), 8.25 (s, 1H), 8.28 (s,1H).

EXAMPLE 16

2-Chloro-6,7-difluoro-3-methylquinoxaline

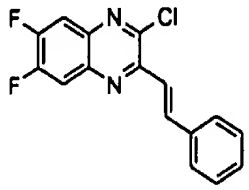


6,7-Difluoro-3-methyl-1H-quinoxalin-2-one (2 g, prepared similarly as described above from 4,5-difluoro-1,2-phenylenediamine and pyruvic acid) was mixed with $POCl_3$ (20 ml) and 4-dimethylaminopyridine (10 mol%) and the mixture was reflux d for 2 h. The mixture was allowed to cool and poured onto ice (300 ml), filtered and washed with water to afford the title compound.

^{1}H NMR (DMSO-d_6): δ 2.83 (s, 3H), 7.76 (m, 2H)

EXAMPLE 17

2-Chloro-6,7-difluoro-3-styrylquinoxaline



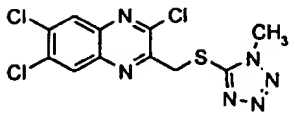
6,7-Difluoro-3-methyl-1H-quinoxalin-2-one (2 g, 10.2 mmol) was dissolved in a mixture of acetic acid glacial (40 ml) and 98% sulfuric acid (4 ml). Benzaldehyde (1.08 g, 10.2 mmol) was added and the resulting mixture was stirred at reflux temperature for 3.5 hours. The mixture was allowed to cool to 85°C and then it was poured onto ice (400 ml). The solid was filtered, washed with water and ethyl acetate and dried *in vacuo* at 30°C over night to afford 2.5 g (88%) of 6,7-difluoro-3-styryl-1H-quinoxalin-2-one.

^{1}H NMR (DMSO-d_6): δ 7.20 (dd, 1H), 7.4 - 7.5 (m, 3H), 7.57 (d, 1H), 7.73 (d, 2H), 7.85 (dd, 1H), 8.04 (d, 1H), 12.6 (s, 1H).

The above 6,7-difluoro-3-styryl-1H-quinoxalin-2-one (2.65 g, 0.93 mmol) was mixed with 4-dimethylaminopyridine (0.27 g) and $POCl_3$ (27 ml) and the mixture was refluxed for 30 minutes. After cooling, the mixture was poured onto ice (400 ml) and the solid was filtered, washed with water (3 x) and dried *in vacuo* over night. Column chromatography on silica gel, eluting with ethyl acetate:heptane 1:20 afforded 1.6 g (56 %) of the title compound.

^{1}H NMR ($CDCl_3$): δ 7.4-7.5 (m, 3H), 7.65-7.75 (m, 4H), 7.84 (dd, 1H), 8.08 (d, 1H).

EXAMPLE 18

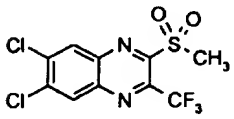


To a solution of 2,6,7-trichloro-3-chloromethyl quinoxaline (500 mg, 1.78 mmol) in 7 ml of DMF was added 5-mercapto-1-methyltetrazole (206 mg, 1.78 mmol) followed by triethylamine (0.25 ml). The resulting dark reaction mixture was stirred at room temperature for five hours. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated. This was concentrated to an oil and was further purified by column chromatography (ethyl acetate:hexanes 1:2) to afford the title compound as a rusty powder.

^{1}H NMR (DMSO-d_6): δ 3.91 (s, 3H), 4.90 (s, 2H), 8.30 (s, 1H), 8.36 (s, 1H).
MS (APCI $(M+H)^+$) m/z 360.9.

EXAMPLE 19

6,7-Dichloro-2-methanesulfonyl-3-trifluoromethylquinoxaline

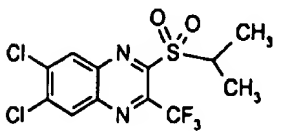


To a solution of 2,6,7-trichloro-3-trifluoromethylquinoxaline (64 mg, 0.2 mmol) in 1 ml of DMF was added sodium methanesulfinic acid (43 mg, 0.4 mmol). The reaction mixture was stirred at room temperature overnight, then it was partitioned between ethyl acetate and water. The organic layer was separated and concentrated to an oil. This oil was further purified by column chromatography (ethyl acetate:hexanes 1:3) to yield the title compound as a white solid.

^{1}H NMR ($CDCl_3$) δ 3.54 (s, 3H), 8.40 (s, 1H), 8.48 (s, 1H).
MS (APCI positive) 344.9.

EXAMPLE 20

6,7-Dichloro-2-trifluoromethyl-3-isopropylsulfonylquinoxaline

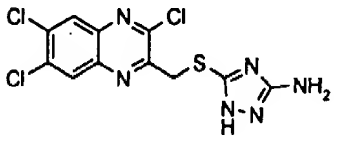


To a solution of 2,6,7-trichloro-3-trifluoromethylquinoxaline (74 mg, 0.25 mmole) in DMF (1 ml) was added isopropyl mercaptan followed by potassium carbonate. The reaction mixture was left at room temperature for 5 hours. Aqueous work-up afforded the desired sulfide as an oil. The oil was dissolved in 2 ml DCE. To this solution was added 3-chloro-peroxybenzoic acid (0.5 mmol). The reaction mixture was left at room temperature for 3 hours followed by aques work-up and column chromatography to yield the title compound as a white solid.

^{1}H NMR ($CDCl_3$): 1.48 (d, 6H), 4.35 (m, 1H), δ 8.39 (s, 1H), 8.47 (s, 1H).
MS (APCI $(M+H)^+$) m/z 372.9.

EXAMPLE 21

5-(3,6,7-Trichloroquinoxalin-2-ylmethylsulfanyl)-1H-1,2,4-triazol-3-ylamine



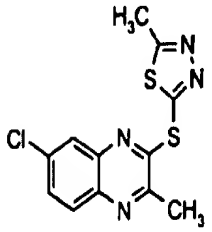
2,6,7-trichloro-3-chloromethyl quinoxaline (105 mg, 0.37 mmol) and 3-amino-5-mercapto-1,2,4-triazole (48 mg, 0.41 mmol) were dissolved in DMF (3 ml). Triethylamine (0.2 ml, 1.1 mmol) was then added and the dark brown solution was allowed to stand at room temperature overnight. After removing the solvent under reduced pressure, the residue was taken up in ethyl acetate and water. The layers were separated and th aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were concentrated *in vacuo*, and the residue was purified by flash column chromatography using ethyl acetate to afford the title compound.

^{1}H NMR (MeOH-d_4): δ 4.61 (s, 2H), 8.17 (s, 2H);

MS (APCI (M+H)$^+$) m/z 360.9.

EXAMPLE 22

6-Chloro-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline



To solution of 4-chloro-1,2-phenylenediamine (5.0 g, 35 mmol) in 100 ml of methanol ethyl pyruvate (4.2 ml, 39 mmol) was added. The mixture was stirred at room temperature for 4 hours. The precipitate was filtered off, washed with methanol and dried to afford 4.95g(73 %) of a 6:4 mixture of 7-chloro-3-methyl-quinoxalin-2(1H)-one and 6-chloro-3-methyl-quinoxalin-2(1H)-one, respectively. A portion of the latter mixture (2.0 g, 10.28 mmol) was reacted with phenylphosphonic dichloride (4.0 g, 20.55 mmol) at 150 °C for 4 hours. The mixture was cooled, water (75 ml) was added and the pH was adjusted to 7 with aqueous ammonia. The precipitate was filtered off and washed with water. The product was purified by flash column chromatography using ethyl acetate:hexanes 1:9 affording 2,6-dichloro-3-methylquinoxaline and 3,6-dichloro-2-methylquinoxaline, respectively.

2,6-Dichloro-3-methylquinoxaline : Pale red solid M.p. 128-29 °C (Litt. M.p. 128-29 °C; Heterocycles 23(8), 2069-2074, 1985).

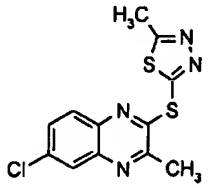
3,6-Dichloro-2-m thylquinoxaline : Red solid M.p. 124-26 °C. ^{1}H NMR (CDCl3): δ 2.85 (s, 3H), 7.69 (dd, 1H), 7.96 (d, 1H), 7.98 (d, 1H).

by flash column chromatography using ethyl acetate:touluene 1:9 to afford 29 mg (47%) of the title compound.

M.p. 194.5-196.5 °C. ^{1}H NMR (DMSO-d_6) δ 2.78 (s, 3H), 2.86 (s, 3H), 7.86 (dd, 1H), 8.08 (d, 1H), 8.17(d, 1H).

EXAMPLE 23

6-Chloro-3-methyl-2-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline

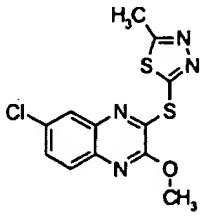


2,6-Dichloro-3-methylquinoxaline was reacted with 2-mercapto-5-methylthiadiazole as described above to yield 18 mg (42%) of the title compound a pale red solid.

M.p. 189-90 °C.^{1}H NMR (DMSO-d_6) δ 2.77 (s, 3H), 2.84 (s, 3H), 7.83 (dd, 1H), 8.07(d, 1H), 8.16 (d, 1H).

EXAMPLE 24

6-Chloro-2-methoxy-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)quinoxaline



A suspension of 2,3,6-trichloroquinoxaline (J. Med. Chem. **33**, 2240-54, 1990) (5.84 g, 25 mmol) in 70 ml of dry methanol was stirred at 50 °C while methanolic sodium methoxide (30 mmol) (prepared from 0.7 g of sodium and 70 ml of dry methanol) was added during 5 hours. When the addition was complete, heating and stirring was continued for further 16 hours.

The mixture was cooled in an ice bath, the precipitate filtered off, washed with a small amount of methanol and dried to afford 4.28 g of a mixture consisting of 2,3-dimethoxy-6-chloroquinoxaline, 2,6-dichloro-3-methoxyquinoxaline and 3,6-dichloro-2-methoxyquinoxaline, respectively.

A 3 g portion of the latter mixture was purified by flash column chromatography using toluene:hexanes 7: 3 as eluent and 3,6-dichloro-2-methoxyquinoxaline was obtained in pure state.

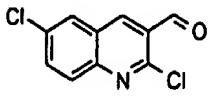
M.p. 113-14 °C (Methanol). ^{1}H NMR ($CDCl_3$) δ 4.18 (s, 3H), 7.54 (dd, 1H), 7.88 (d,1H), 7.89 (d, 1H).

A mixture of 3,6-dichloro-2-methoxyquinoxaline (50 mg, 0.218 mmol), potassium carbonate (31 mg, 0.224 mmol) and 2-mercapto-5-methylthiadiazole (31 mg, 0.219 mmol) in 3 ml of acetone was stirred while cesium fluoride (40 mg, 0.262 mmol) and two drops of dimethylformamide was added. The mixture was stirred and heated at 55 °C for 16 hours. The cooled mixture was filtered and washed with acetone. The organic solution was evaporated and the residue was recrystallised from methanol to afford 13 mg (18%) of the title compound as off white crystals.

M.p. 186-88 °C. ^{1}H NMR ($CDCl_3$): δ 2.90 (s, 3H), 4.20 (s, 3H), 7.52 (dd, 1H), 7.87 (d, 1H), 7.88 (d, 1H).

EXAMPLE 25

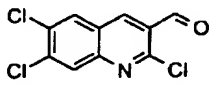
2,6-Dichloroquinoline-3-carbaldehyde



To dimethylformamide (6.5 g, 90 mmol) cooled to 0 °C, $POCl_3$ (31.1 g,210 mmol) was added while the temperature was kept below 5 °C. 4-Chloroacetanilide (5.07 g, 30 mmol) was added in one portion and the reaction mixture was heated to 75 °C for 4 hours. The reaction

EXAMPLE 26

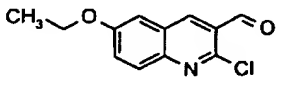
2,6,7-Trichloroquinoline-3-carbaldehyde



The title compound was prepared by the same method as described in example 25 starting from 3,4-dichloro-acetanilid. M.p. 190-91 °C.

EXAMPLE 27

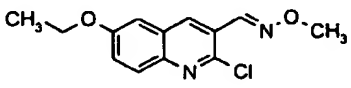
2-chloro-6-ethoxy-quinoline-3-carbaldehyde



The title compound was prepared by the same method as described in example 25 starting from 4-ethoxy-acetanilid. M.p. 163-64 °C.

EXAMPLE 28

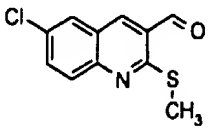
2-Chloro-6-ethoxyquinoline-3-carbaldehyde o-methyl-oxime



To a solution of 2-chloro-6-ethoxyquinoline-3-carbaldehyde (0.235g, 1.0 mmol) in ethanol o-methylhydroxylamine hydrochloride (0.10 g, 1.1 mmol) was added. The reaction mixture was heated to reflux for 0.5 hours. After cooling to room temperature the precipitated compound was filtered and dried. Yield 180 mg. M.p. 142-44 °C.

EXAMPLE 29

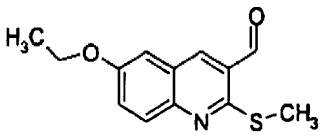
6-Chloro-2-methylsulfanylquinoline-3-carbaldehyde



To a solution of 2,6-dichloro-quinoline-3-carbaldehyde (113 mg, 0.5 mmol) in DMF (5 ml) sodium hydrosulfide hydrate (105 mg,1.5 mmol) and potassium carbonate (250 mg) was added. The reaction mixture was stirred at room temperature for 1 hour. To the reaction mixture methyl iodide (260 mg, 2.0 mmol) was added. Water was added and the separated compound was filtered dried and recrystallized from ethanol. Yield 70 mg. M.p.154-55 °C.

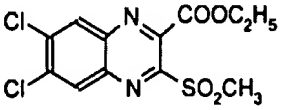
EXAMPLE 30

6-Ethoxy-2-methylsulfanylquinoline-3-carbaldehyde

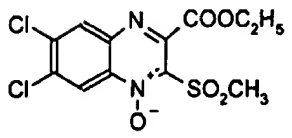


The title compound was prepared as described in example 29 starting from 2-chloro-6-ethoxyquinoline-3-carbaldehyde. M.p. 124-25 °C.

EXAMPLE 31



EXAMPLE 32

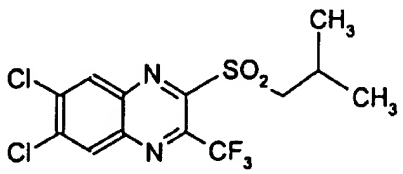


To a solution of ethyl 3,6,7-trichloroquinoxalinyl carboxylate (182 mg, 0.6 mmol) in 2.5 ml of DMF was added $NaHS.2H_2O$ (110.4 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 3 h and was partitioned in water and ethyl acetate. The organic layer was concentrated to a red solid. Without further purification, this red solid was re-dissolved in 3 ml of ethyl acetate. A large excess of MeI (2 ml) was added to the above solution followed by a large excess of TEA (2 ml). The red color instantly became yellowish. Then, the reaction mixture was washed with water once and concentrated to a yellow oil. This oil was dissolved in 2 ml of CH_2Cl_2. To this was added mCPBA (440 mg, 47% pure, 1.2 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated to a solid. This solid was purified by column chromatography with ethyl acetate:hexane (1:3) to yield a mixture of Examples No 31 and 32 in a ratio of 9:1 as white solids. These two compounds were separated by HPLC.

Example No 31: ^1H NMR ($CDCl_3$) δ 1.5 (t, 3H), 3.4 (s, 3H), 4.6 (q, 2H), 8.4 (s, 2H); MS (APCI+) 349.

Example No 32: ^1H NMR ($CDCl_3$) δ 1.5 (t, 3H), 3.6 (s, 3H), 4.5 (q, 2H), 8.2 (s, 1H), 8.4 (s, 1H); MS (APCI+) 365.

EXAMPLE 33

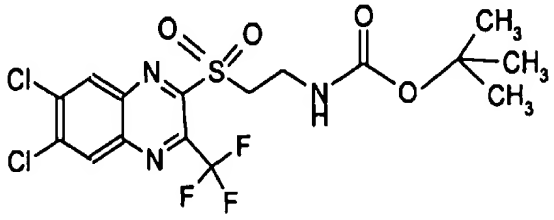


Using the same synthetic procedure as for the synthesis of the compound according to example 20, the title compound was synthesized as white powder.

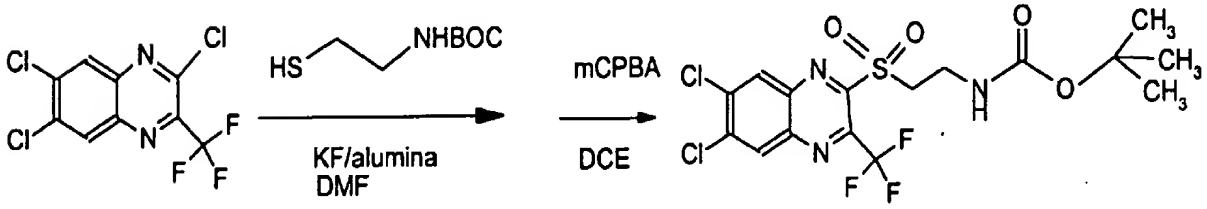
^{1}H NMR ($CDCl_3$) δ 1.2 (d, 6H), 2.5 (m, 1H), 3.6 (d, 2H), 8.4 (s, 1H), 8.5 (s, 1H); MS (APCI+) 387.

EXAMPLE 34

Tert-butyl 2-{[6,7-dichloro-3-(trifluoromethyl)-2-quinoxalinyl]sulfonyl}ethylcarbamate



REACTION SCHEME

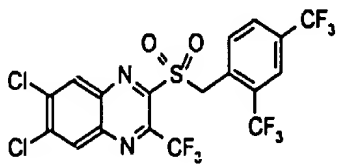


To a solution of 2,6,7-trichloro-3-trifluoromethyl quinoxaline (100 mg, 0.33 mmol) in dimethylformamide (3 ml) was added one small scoop of potassium fluoride over alumina followed by t-butyl N-(2-mercaptoethyl)-carbamate (0.06 ml, 0.37 mmol). The reaction was stirred at room temperature overnight. The solvent was removed by vacuum and the residue was dissolved in ethyl acetate. Water was added, the layers were separated and the aqueous layer was extracted twice with ethyl acetate. After combining and concentrating the organic layers, the crude alkylation product was dissolved in dichloroethane (5 ml), then metachloro p roxybenzoic acid (574 mg, 1.32 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was quenched by addition of a saturated solution

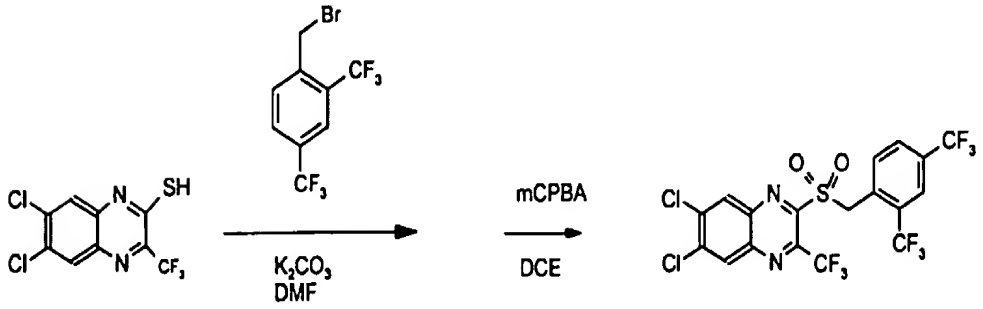
^{1}H NMR ($CDCl_3$) δ 0.39 (s, 9H), 3.80 (m, 2H), 3.99 (m, 2H), 5.20 (brd s, 1H), 8.44 (s, 1H), 8.47 (s, 1H). MS (APCI negative) 472.9.

EXAMPLE 35

2-{[2,4-bis(trifluoromethyl)benzyl]sulfonyl}-6,7-dichloro-3-(trifluoromethyl)quinoxaline



REACTION SCHEME

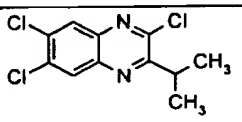
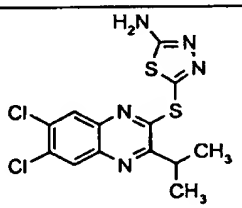
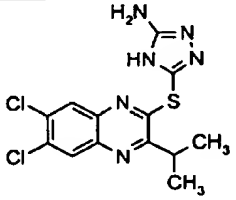
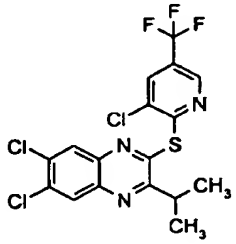


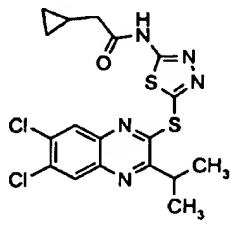
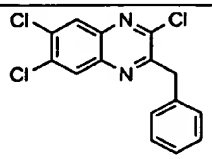
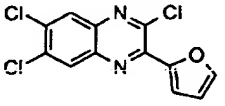
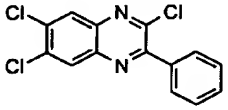
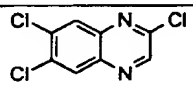
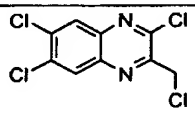
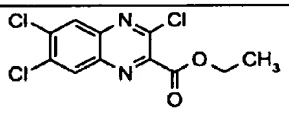
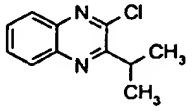
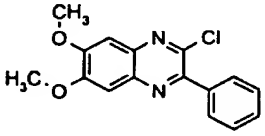
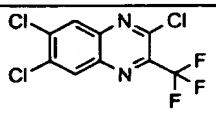
To a solution of 6,7-dichloro-3-trifluoromethyl-2-mercaptoquinoxaline (35 mg, 0.12 mmol) in dimethylformamide (2.5 ml) was added a small scoop of potassium carbonate followed by 2,4-bis(trifluoromethyl)benzyl bromide (0.04 ml, 0.13 mmol). The reaction was stirred at room temperature. After 5 hours, thin layer chromatography showed all starting material was gone. The solvent was removed by vacuum, the residue was dissolved in ethyl acetate and water was added. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and concentrated under reduced pres-

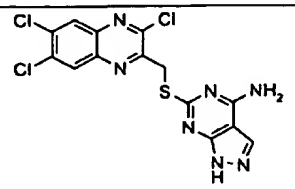
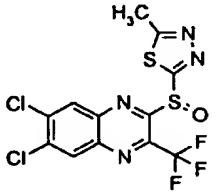
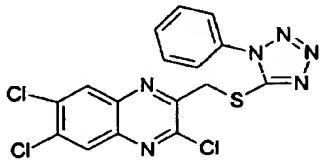
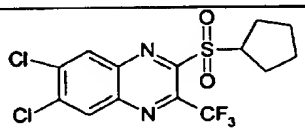
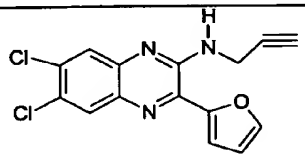
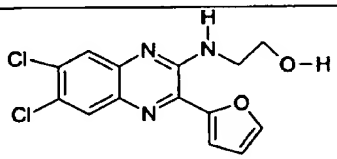
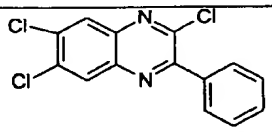
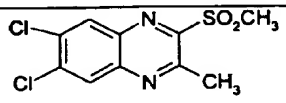
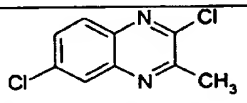
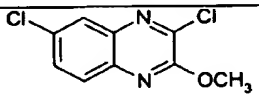
rated solution of sodium bicarbonate. The layers were separated and the aqueous layer was extracted twice with dichloroethane. The organic layers were combined and concentrated under reduced pressure to a pale yellow solid. The product was purified by high performance liquid chromatography.

^{1}H NMR ($CDCl_3$) δ 5.29 (s, 2H), 7.89 (m, 1H), 8.01 (m, 2H), 8.39 (s, 1H), 8.50 (s, 1H). MS (APCI negative) 555.8.

Similarly, the following compounds were made:

Example No	Structure
36	
37	
38	
39	

40	
41	
42	
43	
44	
45	
46	
47	
48	
49	

50	
51	
52	
53	
54	
55	
56	
57	
58	
59	

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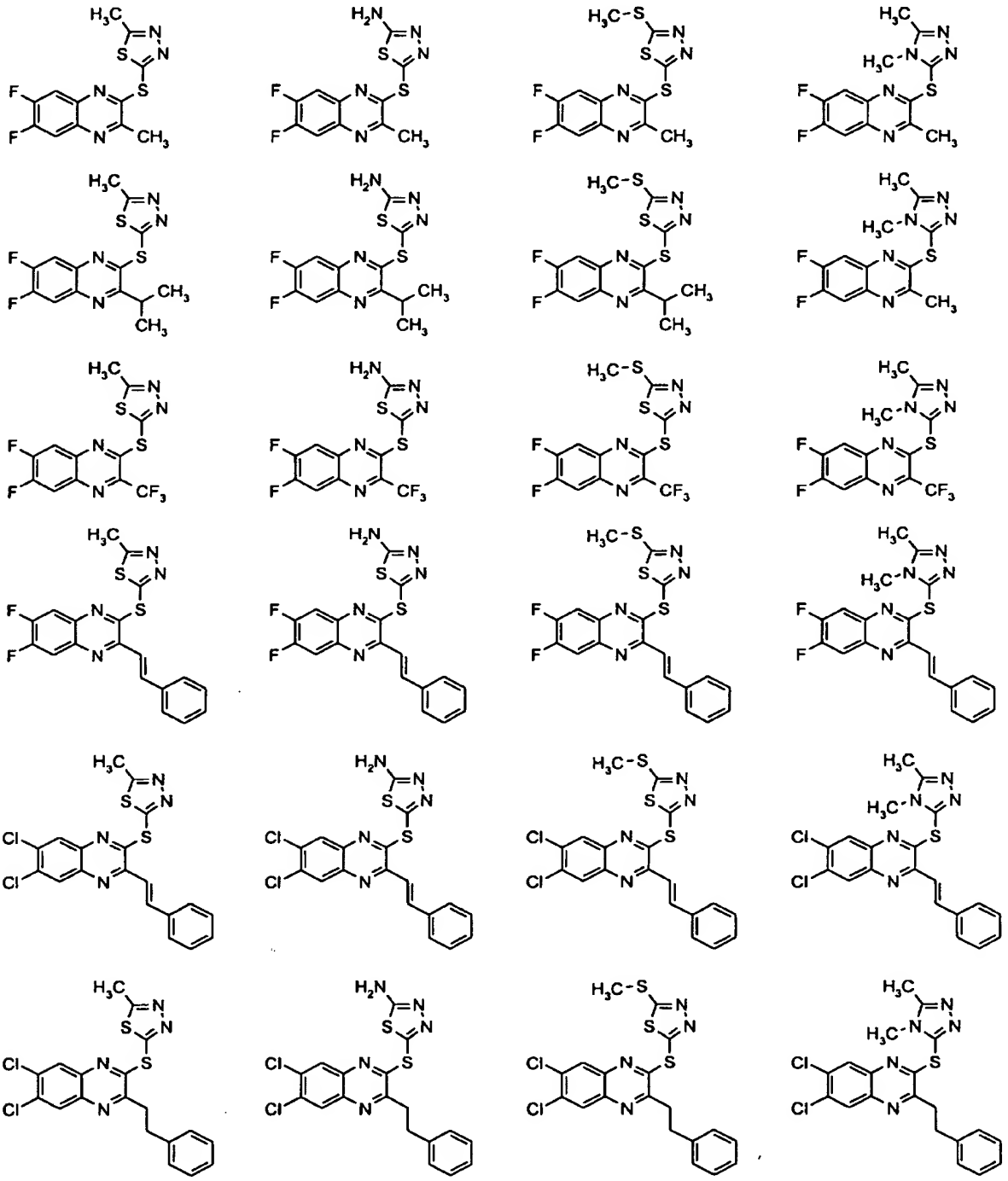

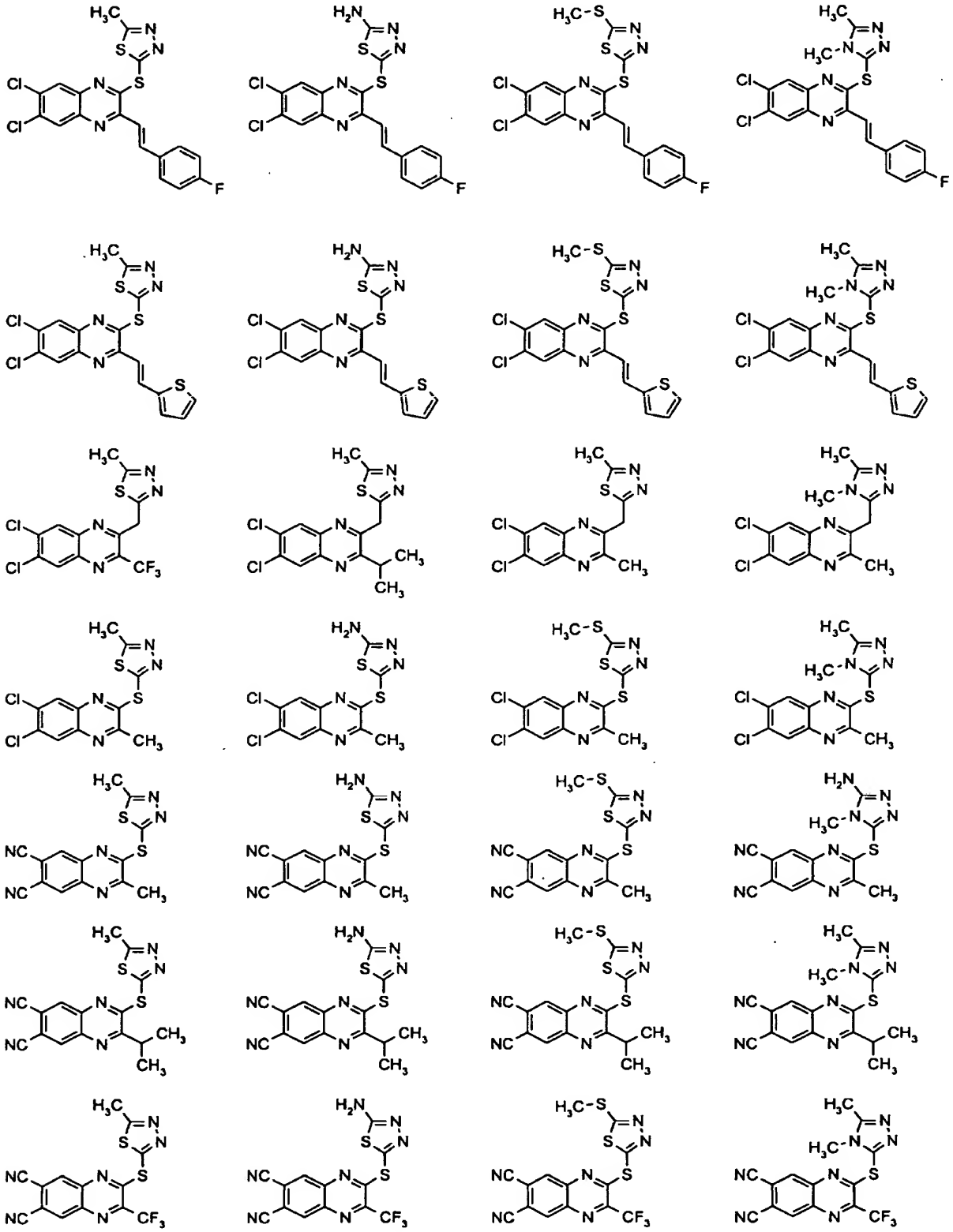

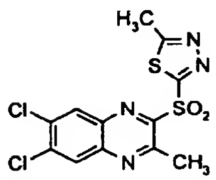
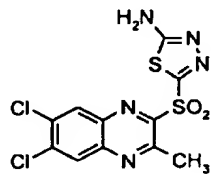
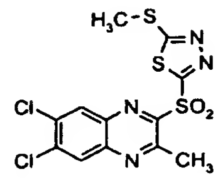
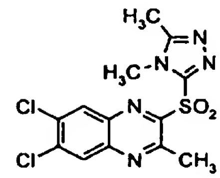

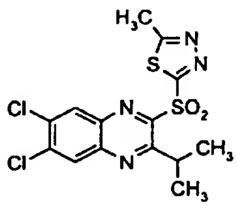
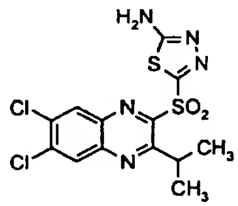
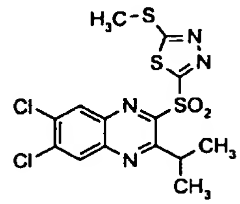
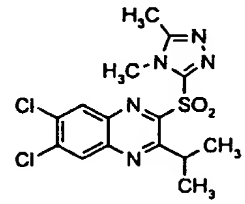

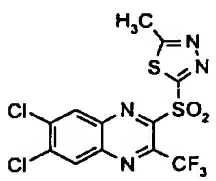
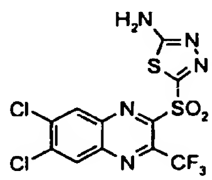
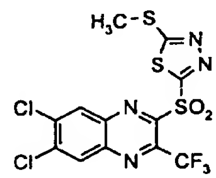
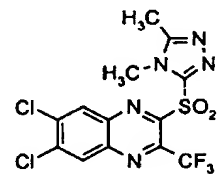

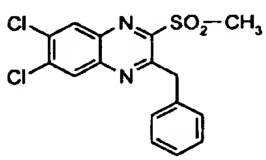
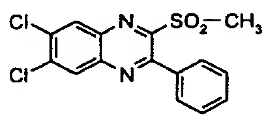

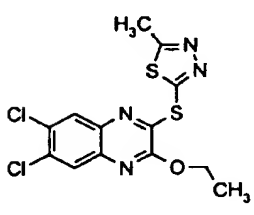
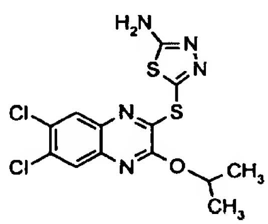
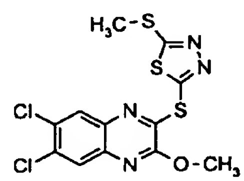
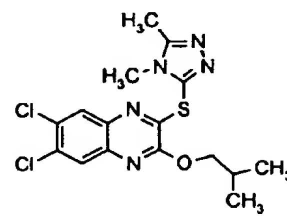

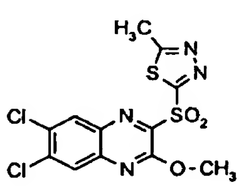
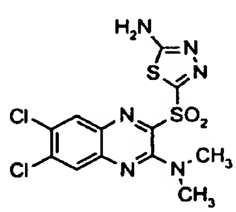
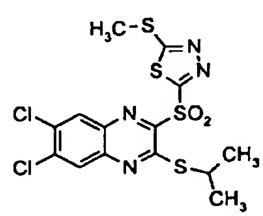
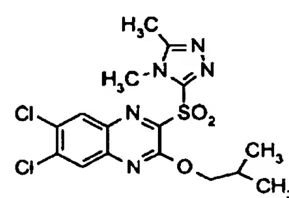

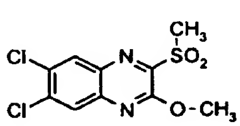
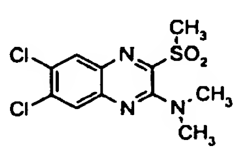
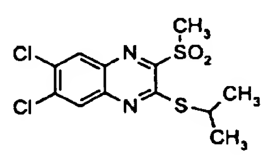
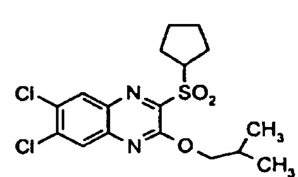

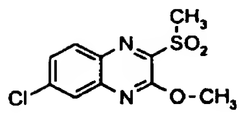
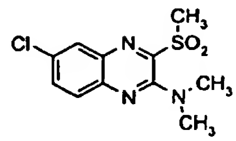
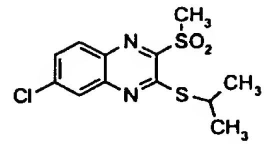
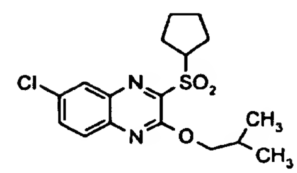
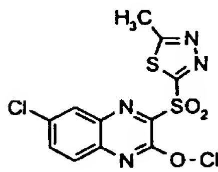
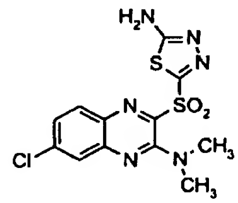
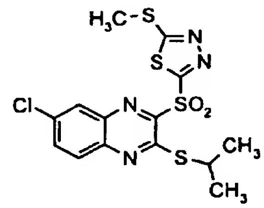
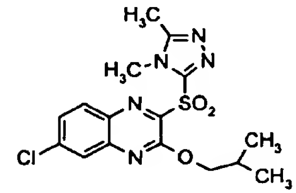
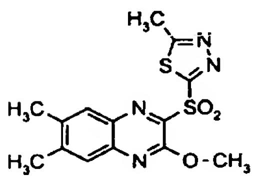
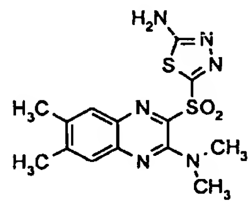
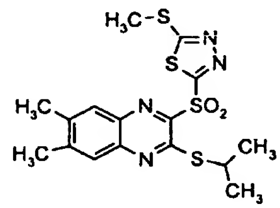
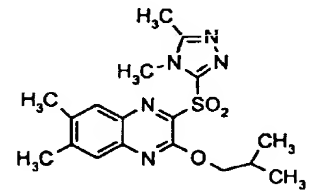
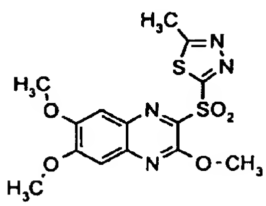
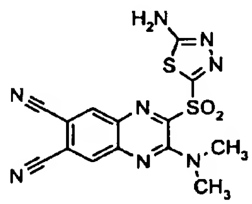
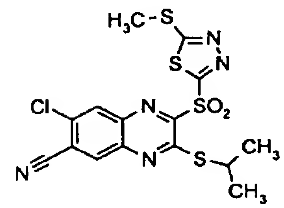
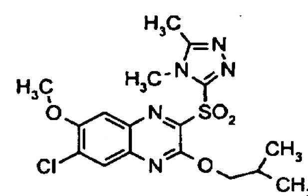
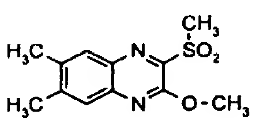
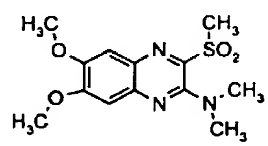
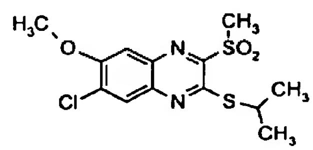

EXAMPLE 61

Determinaton of EC_{50}

Stimulation of cAMP formation in a cell line expressing the cloned human GLP-1 receptor

In order to demonstrate the efficacy of the GLP-1 agonists, their ability to stimulate formation of cAMP in a cell line expressing the cloned human GLP-1 receptor was tested. The EC_{50} value was calculated from the dose-response curve.

Baby hamster kidney (BHK) cells expressing the human pancreatic GLP-1 receptor were used (Knudsen and Pridal, 1996, Eur. J. Pharm. 318, 429-435). Plasma membranes were prepared (Adelhorst *et al*, 1994, J. Biol. Chem. 269, 6275) by homogenisation in buffer (10 mmol/l Tris-HCl and 30 mmol/l NaCl pH 7.4, containing, in addition, 1 mmol/l dithiothreitol, 5 mg/l leupeptin (Sigma, St. Louis, MO, USA), 5 mg/l pepstatin (Sigma, St. Louis, MO, USA), 100 mg/l bacitracin (Sigma, St. Louis, MO, USA), and 16 mg/l aprotinin (Novo Nordisk A/S, Bagsvaerd, Denmark)). The homogenate was centrifuged on top of a layer of 41 w/v% sucrose. The white band between the two layers was diluted in buffer and centrifuged. Plasma membranes were stored at -80°C until use.

The assay was carried out in 96-well microtiter plates in a total volume of 200 µl. The resulting concentration in the assay was 50 mmol/l Tris-HCl, pH 7.4, 1 mmol/l EGTA, 1.5 mmol/l $MgCl_2$, 1.85 mmol/l ATP, 20 µM GTP, 1 mmol/l 3-isobutyl-1-methylxanthine, 0.01 % Tween-20 and 0.1 % bovine serum albumin (Reinst, Behringwerke AG, Marburg, Germany). Compounds to be tested for agonist activity were dissolved and diluted in DMSO. GLP-1 was dissolved and diluted in buffer. For GLP-1 test, diluted compound was added in 35 µl and 10 µl DMSO added extra. For compounds, 10 µl compound in DMSO was added. 1-4 µg plasma membrane in 50 µl was added and the mixture was incubated for 2 h at 37°C. The reaction was stopped by the

Competition binding assay, compounds do not compete with ^{125}I-GLP-1

Plasma membranes were prepared from BHK cells. Binding assays were carried out in polypropylene tubes. The buffer was 25 mM HEPES, 0.1% BSA, pH 7.4. GLP-1 and test compounds were dissolved and diluted as described in Example No 61. Tracer (labelled GLP-1) was prepared as described in (26). Test compound + tracer (30.000 cpm) + plasma membranes (0.5-2 µg) were mixed and tubes incubated at 37°C for 1 hour. Non specific binding was determined with 10^{-7} M GLP-1. Bound and unbound tracer were separated by vacuum filtration. The filters were counted in a γ-scintillation counter. The binding of the tracer in the absence of the test compounds and GLP-1 was set to 100%. A compound which does not compete with GLP-1 in a competition binding assay will not displace the tracer. Therefore, the tracer will display an unchanged binding of 100 % in this assay whereas different concentrations of GLP-1 will compete with the tracer resulting in a decreased binding of the tracer in the range of between 0 and up to 100%.

EXAMPLE 63

Competition binding assay, compounds potentiate binding of ^{125}I-GLP-1

Plasma membranes were prepared as in Example No 61. Binding assays were carried out in polypropylene tubes. The buffer was 25 mM HEPES, 0.1% BSA, pH 7.4. GLP-1 and test compounds were dissolved and diluted as described in Example No 61. Tracer (labelled GLP-1) was prepar d as described in (26). Test compound + tracer (30.000 cpm) + plasma membrane (0.5-2 µg) were mixed and tubes incubated at 37°C for 1 hour. Non specific binding was determined with 10^{-7} M GLP-1. Bound and unbound tracer were separated by vacuum filtration.

Saturation experiments, compounds stabilize another conformation of the receptor than that GLP-1 stabilize physiologically

Plasma membranes were prepared as in Example No 61. Binding assays were carried out in filter microtiter plates (MADV N65, Millipore). The buffer was 50 mM HEPES, 5 mM EGTA, 5 mM $MgCl_2$, 0.005% Tween 20, pH 7.4. GLP-1 and test compounds was dissolved and diluted as described in Example No 61. Tracer (labelled GLP-1) was prepared as described in (26) and diluted in buffer. 165 µl buffer + 10µl DMSO with or without 10 µM 6,7-dichloro-2-trifluoromethyl-3-(5-methyl-1,3,4-thiadiazol-2-ylsulfanyl)-quinoxaline (Example No 2) + 25 µl of different dilutions of tracer + 25µl plasma membrane (0.5-2 µg) was mixed and plates incubated at 25°C for 2 hours. Non specific binding was determined with 10^{-6} M GLP-1. Bound and unbound tracer were separated by vacuum filtration (Millipore vacuum manifold). The plates were washed once with 150 µl buffer/ well, and air dried for a couple of hours, whereupon filters were separated from the plates using a Millipore Puncher. The filters were counted in a γ-scintillation counter. The specific binding (total minus non-specific) was then plotted vs the concentration of tracer added. A curve fitting program (eg the saturation/scatchard template in GraphPad Prism®) then determined the number of binding sites and the affinity. There may be more than one binding site with different affinities. When such an experiment is performed with GLP-1 one may observe one or two different binding sites dependent on the temperature at which the experiment is performed.

EXAMPLE 65

Stimulation of cAMP formation in a cell line expressing the cloned human Glucagon receptor, compounds selective for the GLP-1 receptor

The procedure in Example 61 was followed except a cell line using the human glucagon receptor was used (Discovery and SAR of the first non-peptide Competitive Human Glucagon Receptor Antagonists. P. Madsen et al., Accepted in J.Med.Chem.). In this assay, glucagon was measured with an EC_{50} of 8.4 pM.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention as defined by the appended claims.

References

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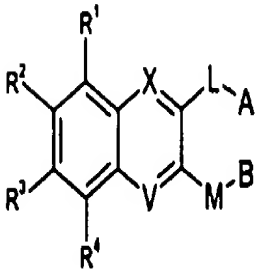
CLAIMS

1. A compound of the general formula (I):



(I)

wherein

R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^5$, lower alkyl, $-SR^5$, $-S(O)_2NR^5R^6$, $-S(O)NR^5R^6$, $-S(O)_2R^5$, $-C(O)NR^5R^6$, $-CH_2OR^5$, $-CH_2NR^5R^6$ or $-C(O)OR^5$;

wherein R^5 and R^6 independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^5 and R^6 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally

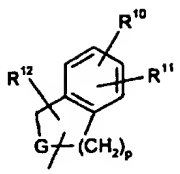
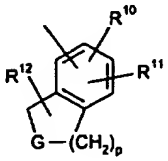
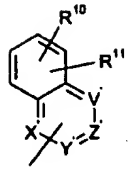
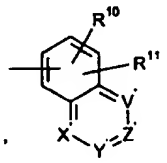
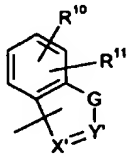
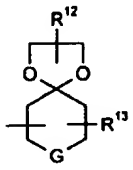
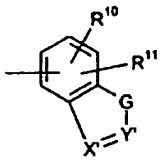
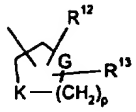
eroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^7 and R^8 together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

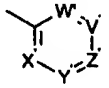
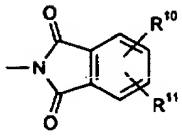
L and M independently are a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mO(CH_2)_n-$, $-(CH_2)_mS(O)(CH_2)_n-$, $-(CH_2)_mS(O)_2(CH_2)_n-$, $-(CH_2)_mCH=CH(CH_2)_n-$, $-(CH_2)_mC\equiv C(CH_2)_n-$, $-(CH_2)_mCHR^9(CH_2)_n-$, $-(CH_2)_mNR^9(CH_2)_n-$, $-(CH_2)_mC(O)NR^9(CH_2)_n-$, $-(CH_2)_mC(O)O(CH_2)_n-$, $-S(CH_2)_mC(O)O(CH_2)_n-$, $-S(CH_2)_mC(O)NR^9(CH_2)_n-$, $-(CH_2)_mOC(O)(CH_2)_n-$, $-(CH_2)_mC(O)(CH_2)_n-$, $-(CH_2)_mC(NOR^9)(CH_2)_n-$, $-(CH_2)_mNR^9S(O)_2(CH_2)_n-$, $-(CH_2)_mS(O)_2NR^9(CH_2)_n-$, $-(CH_2)_mCHOR^9(CH_2)_n-$ or $-(CH_2)_mP(O)(OR^9)O(CH_2)_n-$;

wherein R^9 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl;

m and n independently are 0, 1, 2 or 3;

A and B independently are hydrogen, halogen, $-CF_3$, $-CF_2CF_3$, -CN, $-NO_2$, lower alkyl, lower alkenyl, lower alkynyl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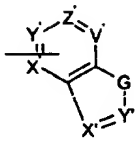


wherein

p is 1, 2 or 3;

X' is -N= or -CR^{14}=;

Y' is -N= or -CR^{15}=;

Z' is -N= or -CR^{16}=;

V' is -N= or -CR^{17}=;

W' is -N= or -CR^{18}=;

G is -NR^{19}-, -O- or -S-;

K is -NR^{20} -O- or -S-;

R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} independently are hydrogen, halogen, -CN, -CF_3, -OCF_3, -OCH_2CF_3, -OCF_2CHF_2, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-

lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, $-SCF_3$, $-SR^{21}$, $-CHF_2$, $-OCHF_2$, $-OS(O)_2CF_3$, $-OS(O)_2R^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)_2R^{21}$, $-S(O)R^{21}$, $-(O)NR^{21}R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$ or $-(O)OR^{21}$, where R^{12} and R^{13} furthermore independently may represent oxo; or two of the groups R^{10} to R^{18} when defined in the same ring together may form a bridge $-OCH_2O-$;

wherein R^{21} and R^{22} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^{21} and R^{22} together with the nitrogen atom to which they are bound form a 3 to 8 membered heterocyclic ring optionally containing one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

$R^{19}$and R^{20} independently are hydrogen, $-OR^{23}$, $-NR^{23}R^{24}$, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl, $-C(O)NR^{23}R^{24}$ or $-C(O)OR^{23}$;

wherein R^{23} and R^{24} independently are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl, cycloalkyl-lower alkynyl, cycloalkenyl-lower alkyl, cycloalkenyl-lower alkenyl, cycloalkenyl-lower alkynyl, aryl-lower alkyl, aryl-lower alkenyl, aryl-lower alkynyl, heterocyclyl-lower alkyl, heterocyclyl-lower alkenyl, heterocyclyl-lower alkynyl, heteroaryl-lower alkyl, heteroaryl-lower alkenyl or heteroaryl-lower alkynyl; or R^{23} and R^{24} together with the nitrogen

one or more further heteroatoms selected from nitrogen, oxygen and sulfur and optionally containing one or more double bonds;

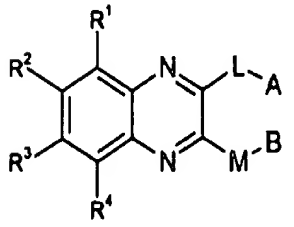
with the provisos that

when L represents a group wherein n is 0, A is not halogen, -CN or $-NO_2$; and

when M represents a group wherein n is 0, B is not halogen, -CN or $-NO_2$;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 of the general formula (II):



(II)

wherein R^1, R^2, R^3, R^4, L, M, A and B are as defined in claim 1.

3. A compound according to claim 1 or 2, wherein R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, lower alkyl, lower alkoxy, $-S(O)_2NR^5R^6$, $-S(O)NR^5R^6$, $-S(O)_2R^5$, $-C(O)NR^5R^6$ or $-C(O)OR^5$, wherein R^5 and R^6 are as defined in claim 1.

4. A compound according to claim 3, wherein R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$ or $-S(O)_2R^5$, wherein R^5 is as defined in claim 1.

5. A compound according to claim 3, wherein R^1, R^2, R^3 and R^4 independently are hydrogen, halogen, -CN, $-CF_3$, lower alkyl, lower alkoxy, or $-C(O)NR^5R^6$, wherein R^5 and R^6 independ-

7. A compound according to any one of the claims 3 to 6, wherein two of the groups R^1 to R^4 are hydrogen and the other two are different from hydrogen.

8. A compound according to claim 7, wherein R^1 and R^4 are both hydrogen.

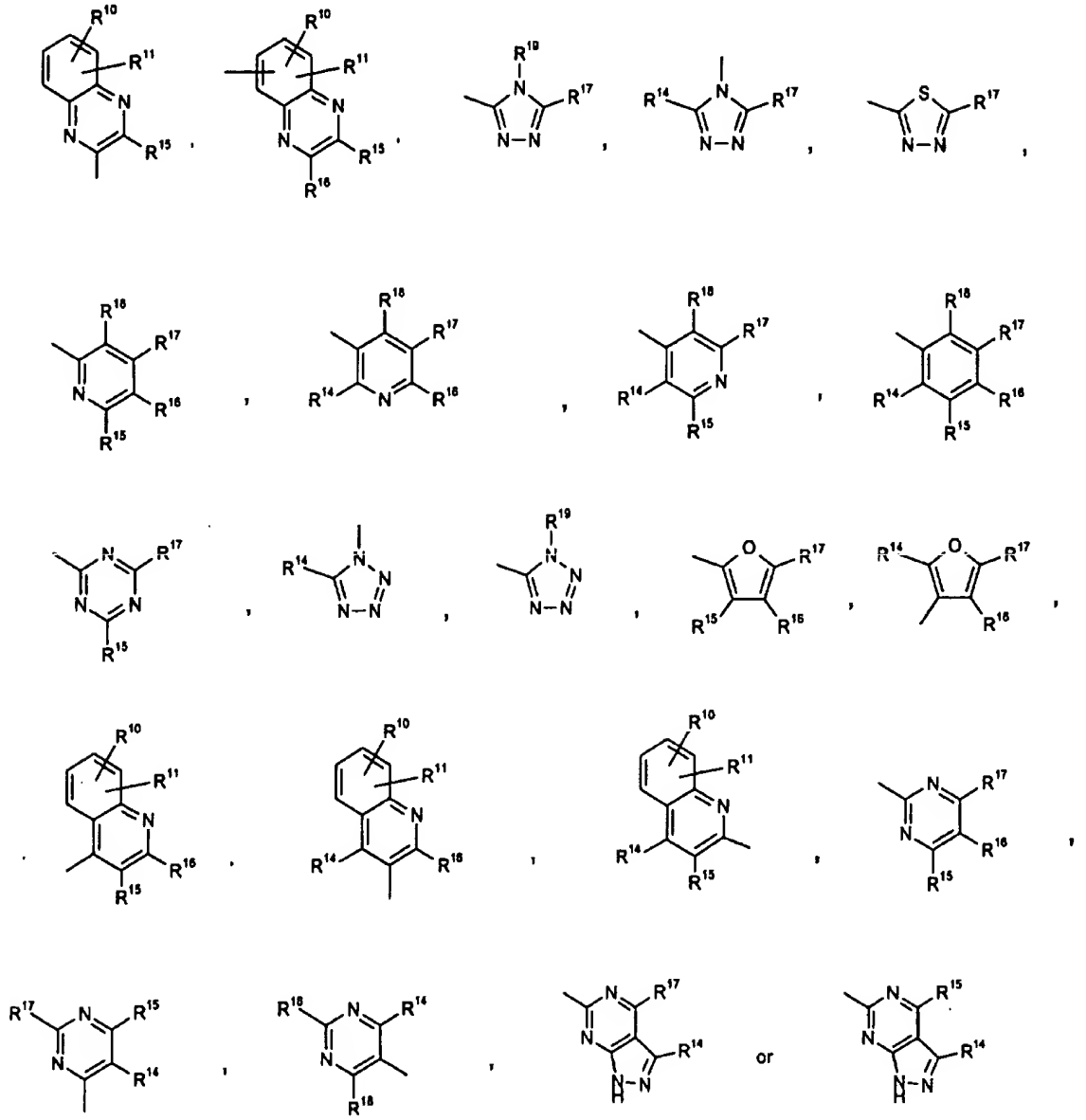
9. A compound according to claim 8, wherein R^2 and R^3 are both halogen.

10. A compound according to any one of the preceding claims, wherein L is a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mS(O)(CH_2)_n-$, $-(CH_2)_mS(O)_2(CH_2)_n-$ or $-(CH_2)_mCHR^9(CH_2)_n-$, wherein m, n and R^9 are as defined in claim 1.

11. A compound according to claim 10, wherein L is a valence bond, $-CH_2-$, $-CH_2S-$, -S-, -S(O)- or $-S(O)_2-$.

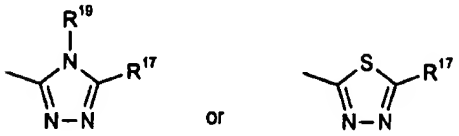
12. A compound according to claim 11, wherein L is -S-, -S(O)- or $-S(O)_2-$.

13. A compound according to any one of the preceding claims, wherein A is lower alkyl, halogen,



wherein R^{10}, R^{11}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are as defined in claim 1.

14. A compound according to any one of the preceding claims, wherein A is lower alkyl,



wherein R^{17} and R^{19} are as defined in claim 1.

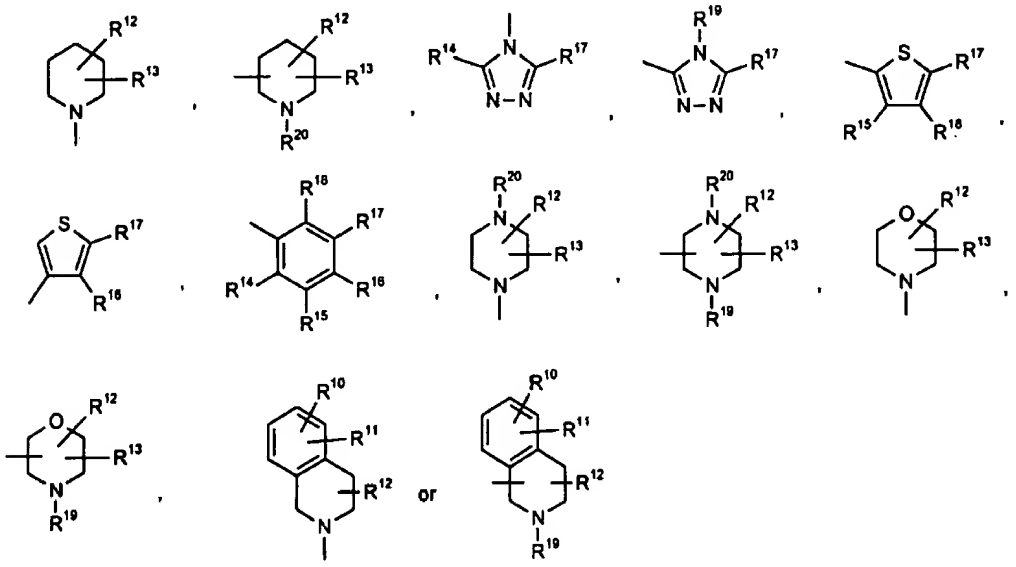
15. A compound according to claim 14, wh rein R^{17} is lower alkyl, $-NH_2$ or -S-lower alkyl and R^{19} is hydrogen.

16. A compound according to any one of the preceding claims, wherein M is a valence bond, $-(CH_2)_mS(CH_2)_n-$, $-(CH_2)_mCH=CH(CH_2)_n-$ or $-(CH_2)_mCHR^9(CH_2)_n-$ wherein m, n and R^9 are as defined in claim 1.

17. A compound according to claim 16, wherein M is a valence bond, $-CH_2S-$, -CH=CH-, $-CH_2CH_2-$ or $-CH_2-$.

18. A compound according to claim 17, wherein M is a valence bond.

19. A compound according to any one of the preceding claims, wherein B is hydrogen, halogen, $-CF_3$, $-CF_2CF_3$, lower alkyl,



wherein R^{12} to R^{20} are as defined in claim 1.

20. A compound according to claim 19, wherein B is $-CF_3$ or lower alkyl.

21. A compound according to claim 2, wherein R^2 and R^3 are both either halogen, -CN or $-CF_3$, L is $-S(CH_2)_n-$, $-S(O)(CH_2)_n-$ or $-S(O)_2(CH_2)_n-$ wherein n is 0, 1, 2 or 3, and R^1, R^4, A, M and B are as defined in claim 1.

22. A compound according to claim 2, wherein L is $-S(CH_2)_n-$, $-S(O)(CH_2)_n-$ or $-S(O)_2(CH_2)_n-$, wherein n is 0, 1, 2 or 3, M is a valence bond, B is $-CF_3$ or isopropyl, and R^1, R^2, R^3, R^4 and A

are as defined in claim 1, with the proviso that when R^1, R^2, R^3 and R^4 are hydrogen, B is isopropyl and L is $-SCH_2-$, A must not be hydrogen.

23. A compound according to claim 2, wherein L is $-S(CH_2)_n-$, $-S(O)(CH_2)_n-$ or $-S(O)_2(CH_2)_n-$, wherein n is 0, 1, 2 or 3, at least one of the groups R^2 and R^3 are -CN, and R^1, R^4, A, M and B are as defined in claim 1.

24. A compound according to claim 2, wherein L is $-S(CH_2)_n-$, $-S(O)(CH_2)_n-$ or $-S(O)_2(CH_2)_n-$, wherein n is 0, 1, 2 or 3, R^1, R^2, R^3 and R^4 are as defined in claim 1, A is a heterocyclic ring, and

M is $-CH_2S-$, -CH=CH-, $-CH_2CH_2-$ or $-CH_2-$, and B is as defined in claim 1, or

M is a valence bond, and B is $-CF_3$, -CN, lower alkyl, lower alkenyl, lower alkynyl or halogen.

25. A compound according to any one of the claims 1 to 24 characterised by having a molecular weight of up to 1000, preferably of up to 600.

26. A compound according to any one of the claims 1 to 25 characterised by having an EC_{50} value as determined by the method for determining the ability to stimulate cAMP formation in a cell line expressing the cloned human GLP-1 receptor disclosed herein of less than 25 µM,

31. A non-peptide agonist according to any one of the claims 27 to 30 which is a full agonist.

32. A non-peptide agonist according to any one of the claims 27 to 30 which is a partial agonist having an E_{max} of less than 100%, preferably less than 90%, more preferably less than 80%, and even more preferably in the range of 35 to 75% of that of GLP-1.

33. A non-peptide agonist according to any one of the claims 27 to 32 which has at least a 10 fold selectivity towards the human GLP-1 receptor compared to the human glucagon receptor and/or the human GIP receptor.

34. A compound according to any one of the claims 1 to 33 for use as a medicament.

35. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 33 together with one or more pharmaceutically acceptable carriers or excipients.

36. A pharmaceutical composition according to claim 35 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 33.

37. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases wherein an activation of the human GLP-1 receptor is beneficial.

38. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of a metabolic disorder wherein an activation of the human GLP-1 receptor is beneficial.

39. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of IGT.

40. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

41. Use according to claim 40 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

42. Use according to claim 40 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

43. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

44. Use according to any one of the claims 37 to 43 in a regimen which additionally comprises treatment with another antidiabetic.

45. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of obesity.

46. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of obesity in a regimen which additionally comprises treatment with another antiobesity agent.

47. Use of a compound according to any one of the claims 1 to 33 for the preparation of a medicament for the treatment and/or prevention of an appetite regulation or energy expenditure disorder.

48. A method for the treatment and/or prevention of disorders or diseases wherein an activation of the human GLP-1 receptor is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 33 or a pharmaceutical composition according to claim 35 or 36.

49. The method according to claim 48 wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

ABSTRACT

NON-PEPTIDE GLP-1 AGONISTS

Novel non-peptide GLP-1 agonists, pharmaceutical compositions comprising them, use of the non-peptide GLP-1 agonists for the preparation of pharmaceutical compositions and methods for the treatment and/or prevention of disorders and diseases wherein an activation of the human GLP-1 receptor is beneficial, especially metabolic disorders such as IGT, Type 1 diabetes, Type 2 diabetes and obesity.